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THE VASCULAR AND CELLULAR DYNAMICS OF SHOCK.*

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The phenomena of shock have both fascinated and baffled physicians for more than a century. Few conditions of disease have been subjected to more diversified or more penetrating investigations than this, yet final clarification has been delayed. We shall not review the attempts to solve this enigma nor summarize the resulting contributions of factual evidence. Rather, we shall inquire why diligent efforts have led to divergent interpretations. An analysis of the causes for disagreement may be more illuminating than a reëxamination of the existing data.

Shock has been our chief interest for many years, during which we have retraced many trails left by our predecessors and have made several excursions into regions not hitherto explored. More than 400 animals have been used in experiments on various phases of the problem, and the antemortem features of shock have been compared with the necropsy findings in more than 100 clinical cases. This statement merely indicates that the material studied was adequate in amount. Out of these experiences has grown the conviction that the conflicting interpretations of shock have originated from four major sources. Attention is invited successively to each of these causes for confusion.

Circulatory Failure of Capillary Origin. Deficiency of knowledge concerning the functions and reactions of capillary endothelium was the first major hindrance to a comprehension of shock. A clearer understanding of capillary physiology (Krogh[17]), and of the related mechanisms of water balance and cell permeability, has removed

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this hindrance and has illuminated many processes which formerly were obscure. A brief reference to capillary reactions is essential to the discussions which follow.

Each organ and tissue has a supply of capillaries adequate to its maximal circulatory needs. In resting or inactive tissues most of these are contracted and bloodless, while in functioning tissue they are hyperemic. Barcroft[2] showed that muscles during activity require 20 to 40 times more blood than when at rest. Functioning cells consume oxygen and liberate products of metabolism and since capillary endothelium is delicately susceptible to lack of oxygen, the walls relax and the endothelium becomes more permeable whenever moderate anoxia develops. This relaxation allows an increased flow of arterial blood, supplying oxygen and other nutrients. Fresh arterial blood contains a hormonal substance, perhaps of pituitary origin, which causes the capillaries again to contract. This limits the flow of blood until lack of oxygen and/or the accumulation of metabolites again causes relaxation. Thus the local circulatory cycle is repeated at a rate commensurate with the functional activity of the cells.

Endothelium, which is very sensitive to anoxia and to metabolites, is highly susceptible to other agents also. Heidenhain,[14] some 50 years ago, discovered that peptone will produce a decline in blood pressure accompanied by an increased flow of lymph when given intravenously to dogs. He found that extracts of various marine animals and of normal tissues, as liver, pancreas, mucosa, muscle and others, produced the same effects. He noted that both the volume and the protein content of the lymph were increased while total solids of the blood were increased and its plasma volume was decreased. The latter change is now designated by the term *hemoconcentration*. He stated that these effects are characteristic of the action of these "lymphagogues" and attributed them to increased secretory activity of the endothelium.

After the lapse of half a century, increased knowledge of capillary physiology has revealed the full significance of Heidenhain's observations. The increased flow of lymph, its high protein content, the declining blood pressure, the decreased plasma volume and the hemoconcentration, result from the leakage of plasma through endothelium rendered abnormally permeable by the effects of the agents used. Many other substances have been shown to produce the same effects. These include certain alkaloids, diphtheria toxin, tuberculin and other bacterial products, foreign proteins and products of protein cleavage, histamine, bile and cholic salts, venoms and many drugs, chemicals and poisons. These agents have been called capillary poisons for they have one property in common—that of producing relaxation and increased permeability of capillary endothelium.

These reactions illuminate a type of circulatory disturbance

which hitherto was imperfectly understood. The effects described tend to create a disparity between the volume of blood and the volume capacity of the vascular bed. Dilatation of the capillaries and venules *increases the volume capacity*, while leakage of plasma through the capillary wall *lowers* the *total blood volume*. This disparity, if marked, impairs the systemic circulation and produces characteristic morphologic changes in the viscera. The latter consist of dilatation and engorgement of capillaries and venules, petechial hemorrhages resulting from endothelial dissolution, stasis as shown by compact masses of corpuscles in the minute vessels, edema of soft tissues and acute granular degeneration, often accompanied by focal necroses, in parenchymatous organs.

Incipient disparity between the volume of blood and the volume capacity of the vascular bed is compensated for by physiologic reactions. Impulses, probably originating in the carotid sinus, activate the sympatho-adrenal system. The systemic action of adrenalin stimulates the myocardium, mobilizes glucose from the liver, contracts the peripheral arteries, and causes the discharge of reserve blood from the spleen and other reservoirs. So long as this compensation is adequate, there is no ominous decline in the arterial blood pressure, but the latter is maintained at the expense of volume flow. When finally the mechanism of compensation becomes inadequate, the blood pressure declines progressively and the circulatory deficiency is manifested clinically.

Clinical Features. Prostration is evident; the patient is profoundly depressed, weak and restless. The pulse is rapid, feeble and of small volume. The extremities are cold and the body temperature is low. The face is drawn, ashen or livid in color, anxious in expression, and moist with cold sweat. The eyes are sunken and surrounded by bluish rings, producing the classical "Hippocratic facies." Thirst is incessant, but attempts to relieve it are ineffective because of vomiting. The fluid vomited is often in excess of that swallowed and it usually contains small brown flocculi. Perspiration is profuse, and there may be diarrhea. The respirations are shallow and interspersed with deep sighs. Urination is scanty or suppressed. The blood pressure declines progressively. Consciousness is retained until finally there is loss of sensitivity, of responsiveness to stimuli and of reflexes. Unconsciousness or coma precedes death.

The clinical syndrome just described is accompanied by an equally characteristic group of departures from physiologic constants. These are: a reduced total and effective blood volume; a reduced minute volume cardiac output and volume flow of arterial blood; hemoconcentration, increased non-protein nitrogen, glucose and potassium content of the blood; reduced metabolism, alkaline reserve, chloride and oxygen content, and delayed coagulability of the blood. An increased flow of lymph from the thoracic duct is

an early and constant feature when this condition is produced experimentally.

Fluid Balance. Hemoconcentration, which means an increase in the ratio of erythrocytes to plasma per unit volume of blood, is a highly significant feature in the pathologic physiology of shock. Sherrington,[28] Crile,[6] Henderson[15] and other early investigators noted this phenomenon in experimental shock; Cobbett,[5] King[16] and Vale[30] recorded its occurrence in surgical shock. During the previous World War it was found that hemoconcentration was the earliest detectable sign of shock in wounded soldiers (Cannon[4]). The erythrocytic counts ranged from about 6,000,000 in mild cases to over 9,000,000 in severe shock. These cases were differentiated from the effects of hemorrhage by the *dilution* of blood resulting from the latter. A survey of the recorded observations[21d] indicates that the blood regularly becomes concentrated as circulatory failure of capillary origin develops. This results from loss of plasma volume incident to leakage of fluid into the tissue spaces, due to abnormal permeability of the endothelium. It is integrally related to the increased flow of lymph discussed previously and also to the development of edema. It appears that these phenomena occur whenever and however the endothelium in an extensive visceral area is damaged.

Any type of injury to endothelium renders it abnormally permeable to plasma, and, if extensive, it deranges seriously the mechanism of water balance and of absorption. The movement of fluid between the blood and the tissues depends upon the action of several factors, including capillary blood pressure, osmotic pressures, electrolytic concentrations, hormonal substances and others. *But the presence of a normal semipermeable membrane, the endothelium, is absolutely essential to the action of these forces in preserving a physiologic relationship between intravascular and extravascular fluids.* So long as the endothelium is able to perform its part in the maintenance of fluid balance, no hemoconcentration occurs. A change in the permeability of the endothelium deranges the processes by which both blood volume and concentration are maintained at physiologic levels. A significant increase in the concentration of the blood is of grave importance for it indicates a derangement in the vital mechanism of water balance.

Increased Cellular Permeability. This plays a rôle in the pathologic physiology of shock, not less significant than endothelial permeability. Students of cell physiology (Lucké and McCutcheon's[19] review) have shown that the outer protoplasmic surface of each living cell functions as a semipermeable membrane and that, by virtue of this, each cell behaves as an osmotic unit. Some property possessed by living protoplasm maintains chemical concentrations within the cell, differing markedly from those of the external fluid (Gamble[12]). Some of these are shown in Diagram 1:

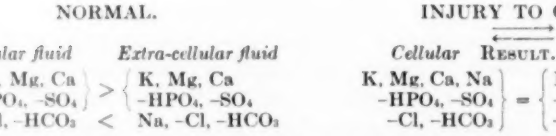

DIAGRAM 1.—The ability to maintain normal differences in concentrations is reduced by any kind of cellular injury and is lost entirely as the cell dies. This allows electrolytes to pass freely from the region of the higher concentration to that of the lower, thus tending to equalize the differences in composition.

For example, the cellular and extracellular fluids differ widely in their normal content of potassium, the approximate degree of which is shown in the following ratio:

$$K\ (Cellular) : K\ (Extra\text{-}cellular) = 21:1$$

The extracellular fluids have been estimated as 15% of the body weight. A simple computation, on the basis of these figures, indicates that complete equalization in the ionic concentrations would result in raising the potassium content of the extravascular fluids to approximately 18 times its normal level. None of the published data, on chemical alterations in the blood during shock, have shown such a high potassium content as this. It is evident that this maximal level could only be reached by *complete* equalization of the chemical concentrations, which condition probably would occur at or after death. Cellular injury tends to allow equalization in the concentration of other ions as well.

Scudder[25] suggested that the high potassium content of the plasma and interstitial fluid *caused* cellular injury and thus was an important etiologic factor. However, his data show that hemoconcentration *precedes* the chemical changes. This indicates that the latter are effects rather than causes.

The same injurious agents, which disturb the fluid balance by affecting the endothelium, may also disturb chemical concentrations by increasing cellular permeability. The former effects result in shock accompanied by hemoconcentration; the latter effect provides a satisfying explanation for the accompanying chemical alterations in the plasma and tissue fluids. The constancy of cellular environment, *physiologic homeostasis* (Cannon[4]), is destroyed and the mechanism for its restoration is vitally deranged. This disturbance of electrolytic balance is scarcely less serious than the associated disturbances of the circulation and of fluid balance.

Few conditions of disease have a more typical clinical picture, more significant physiologic pathology and more characteristic visceral changes than those depicted. They are the clinical and pathologic features which are distinctive of circulatory failure of capillary origin. The term *shock* is commonly used to denote this syndrome. It may be defined in physiologic terms as *a type of circulatory failure, not central but peripheral in origin, characterized by decreased blood*

volume, decreased volume flow and by hemoconcentration. This type of circulatory failure may develop after severe traumatic injury, prolonged or complicated surgical procedures, and after extensive burns of the skin. It occurs also incident to abdominal emergencies such as strangulation, perforations, intestinal infarction, pancreatitis, and it is seen in intoxications, infections of unusual severity, serum disease and in acute poisoning of diverse kinds. The same syndrome may be produced experimentally by trauma, intestinal manipulation, burns and by other forms of tissue abuse in animals or by the injection of various capillary poisons previously referred to.

When this syndrome results from traumatic injury, extensive surgery or tissue abuse, it is usually complicated by hemorrhage and by other factors; but it can be produced in uncomplicated form by various agents which cause endothelial damage. The mechanism of this type of circulatory disturbance may be shown diagrammatically. Most important in that mechanism are the two major factors, *capillary atony* and *anoxia* which, because of their reciprocal effects, give this mechanism the self-perpetuating quality of a vicious circle (Diagram 2).

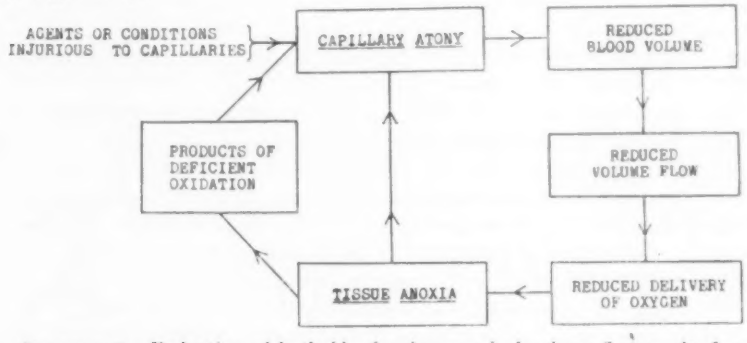

DIAGRAM 2.—Reduction of both blood volume and of volume flow results from dilatation and abnormal permeability of capillaries. A reduced delivery of oxygen causes anoxia in the tissues. Lack of oxygen of itself causes dilatation and permeability of capillaries. This relationship gives the mechanism the character of a vicious circle.

In my opinion, the greatest obstacle to agreement has been that many regard *traumatic shock* as a separate entity, a disease condition *sui generis*. They have recognized no kinship between it and shock originating otherwise, nor have they sensed the importance of endothelial damage as an etiologic factor. Traumatic shock has this factor in common with shock from other causes. Hence many of the items of deranged physiology are identical, regardless of what conditions produced the endothelial effects.

A comprehension of these phenomena had to await an adequate understanding of endothelial reactions and capillary function. Studies on capillary physiology removed one major hindrance to a

comprehension of circulatory failure originating in the capillaries. Another major cause for confusion now awaits consideration.

Shock and the Effects of Hemorrhages. A decline in arterial blood pressure has long been regarded as the central feature in the syndrome of shock. Consequently every single factor which might account for the low blood pressure has been advocated as the primary cause. Myocardial weakness, vasomotor exhaustion, adrenal deficiency, acapnia, fat embolism and hemorrhage—each was proposed and, with the exception of hemorrhage, each was discarded because of incompatibility with known facts.

Space is lacking to review these theories and the facts which rendered each of them untenable. A new interpretation of shock resulted from evidence collected during the previous World War. As experiences with battle wounds accumulated, the conviction grew that absorption of products from injured tissues was a major factor in producing the circulatory deficiency. Surgeons testified that this deficiency was out of all proportion to the apparent severity of the wound and that it subsided in a remarkable fashion after débridement or amputation of the damaged limb.

"The explanation which had the strongest support, both from clinical observations and laboratory studies, was that of a toxic factor, arising from damaged and dying tissue and operating to cause an increased permeability of the capillary walls and a consequent reduction of blood volume by escape of plasma into the lymph spaces. Thus the concentration of the corpuscles is also readily explained."[20]

Many factors contributed to the development of shock from wounds. Among these were hemorrhage, cold, delay in débridement or amputation, anesthesia, infection, improper splinting, rough transportation, loss of fluid by perspiration and by vomiting, and other items.

For several years this explanation of "traumatic toxemia" was widely accepted for it explained satisfactorily most of the observations on shock and it coincided with what was known of capillary reactions at that time.

Then the experiments and interpretations of several groups raised grave doubts concerning the accuracy of that explanation. Dogs were anesthetized deeply and their muscles were severely traumatized by bruising. Blood pressure readings were the sole criteria of shock. After death the amounts of blood and fluid, extravasated into the traumatized areas, were estimated and compared with the calculated blood volumes of the animals. In several series of such experiments, sufficient blood and fluid was found in the traumatized regions to account for the declining blood pressure and the death of the dogs without resort to the supposition that injurious substances had been absorbed from the damaged tissues.

In one group of experiments, the local extravasations of blood and

fluid ranged from 310 to 1057 gm. These represent serious hemorrhages indeed for dogs of average size. The traumatized limbs contained massive extravasations while the adjacent tissues were swollen and infiltrated with bloody fluid. The viscera as seen postmortem were pale and ischemic. In view of these findings and of the *hemodilution* which preceded death, one must concur heartily in the authors' conclusions that hemorrhage was the predominant factor *in these experiments*. Any effects of absorption were so overshadowed by the effects of hemorrhage that they were unrecognizable.

The same method of experimentation produced similar results at the hands of other groups. These agreed in concluding that all the manifestations of traumatic shock are due to local loss of blood and fluid and that absorption of products from traumatized tissues is not a factor.

In 1932 attention was called[22] to several important differences, both physiologic and morphologic, between shock and the effects of hemorrhage. That evidence was amplified and repeated several times in subsequent publications. Yet the belief prevails widely that all the manifestations of shock may result from simple hemorrhages alone. The evidence supporting this belief requires critical examination.

No one has published a detailed comparison of shock with the effects of hemorrhage, yet many significant features of these conditions have been contributed by different workers. They present several points of similarity, because any type of circulatory deficiency evokes compensatory reactions by the sympatho-adrenal system.

Similarities Between Shock and the Effects of Hemorrhage.

Activity of the sympatho-adrenal system causes:
- Stimulation of myocardium; strong rapid pulse in early stages.
- Peripheral vasoconstriction; reduced volume flow; peripheral ischemia and declining temperature; loss of tissue turgor.
- Discharge of reservoir blood into systemic circulation; contraction of spleen.
- Increased blood sugar.
- Dilatation of pupils, often perspiration.

Low basal metabolism.
Decreased alkaline reserve.
Decreased serum protein.
Increased respiratory rate, thirst.
Declining arterial blood pressure (in late stages).
Death due to inadequate circulatory function.

The reactions enumerated are the same in either case, which fact explains several clinical resemblances between shock and hemorrhage. Because of these resemblances, it was assumed that the

two conditions are identical. But a more penetrating scrutiny reveals other totally different departures from physiologic constants. For purposes of comparison, these are arranged in tabular form.

Items.	*Shock.*	*Hemorrhage.*
Endothelium	Permeable to colloids	Impermeable to colloids
Tissue fluid	Increased	Decreased
Flow of lymph	Increased	Decreased
Fluid balance	Disturbed	Undisturbed
Pulmonary edema	Progressive	None
Absorption, gastro-intestinal	Impaired	Unimpaired
Absorption, from tissues	Impaired	Unimpaired
Vomiting	Persistent	No vomiting
Diarrhea	Frequent	Absent
Transfusion of blood	Often ineffective	Effective
Saline solutions, intravenous	Ineffective	Often effective
Blood:		
Hemoglobin, erythrocytes	Increased	Decreased
Specific gravity	Increased	Decreased
Non-protein nitrogen	Increased	Decreased or unchanged
Potassium	Increased	Terminal increase
Calcium	Increased	Decreased
Magnesium	Increased	Decreased
Chlorides	Decreased	Unchanged
Coagulation time	Lengthened	Shortened
Urine	Concentrated, low volume, albumin, erythrocytes, casts, urobilinogen, acetone	No characteristic changes
Necropsy findings:		
Edema	Characteristic	None
Serous effusions	Present	Absent
Capillo-venous congestion	Characteristic	Absent
Petechiæ	Characteristic	Absent
Visceral ischemia	Absent	Present
Organ weight	Increased	Decreased
Gastro-intestinal tract	Dilated, atonic	Contracted
Parenchymal necroses	Present	Absent

It seems remarkable that such noteworthy differences should have escaped the attention of those who have written extensively on the effects of hemorrhages as related to shock. Let it be emphasized that hemorrhage or local loss of fluid is a highly important factor contributing to shock but the assumed identity of these conditions and of their *modus operandi*, is incongruous with a mass of physiologic evidence.

Failure to distinguish between shock and the effects of hemorrhages was the second major cause for conflicting interpretations.

Sources of Error in Mode of Experimentation. Attention is now invited to the third major cause for confusion, comprising sources of error inherent in the method of experimentation. On first entering this much disputed territory, my associates and I followed the paths travelled by our predecessors, including the mode of experimentation. The method in common use was to anesthetize an animal deeply with barbital or otherwise and then to inflict some form of trauma, using records of the arterial pressure as an index of

circulatory effects and of the animal's condition. In one of our earliest experiments, a dog was given sodium phenobarbital intravenously, 0.3 gm. per kilogram, and an artery was cannulated for kymographic record. Although no trauma had as yet been done, the pressure began a progressive decline of 93 mm. Hg within 2 hours. We immediately abandoned barbital as an anesthetic and lost much of our confidence in conclusions based upon such experiments. Evidently our predecessors had had similar experiences for several authors reported that some of their dogs developed "spontaneous shock" under barbital anesthesia. Blalock[3] stated: "In several animals there was a rapid decline in the blood pressure shortly after giving the barbital. These experiments were discarded. The level of the mean blood pressure was used as a criterion of the degree of shock." This statement implies that, if experimentation had begun before barbital caused the pressure to fall, the results of those experiments were considered dependable.

Gruber and Baskett[13] reported that barbital and sodium phenobarbital, in doses comparable to those used in experimental work, caused a fall in blood pressure in 162 out of 164 tests. Seevers and Tatum[26] confirmed the effects of these drugs upon the circulation. Medical military records show that frequently a wounded soldier, whose condition was not critical, developed profound shock immediately when anesthetized for operation. Dale[7] and his associates produced fatal shock in etherized cats by injections of 1 or 2 mm. of histamine, but unanesthetized cats withstood 10 times that dosage. Complete anesthesia, while usually insufficient to produce circulatory failure of itself, comes dangerously near the threshold level in many instances. The barbiturates in the dosage used for anesthesia in animals approach the danger point closely.

It seems remarkable that investigators have overlooked the effects of deep narcosis upon the blood pressure. When variations in pressure are used as a criterion of shock, the importance of this factor of error is incalculable. It appears that the depressor effects observed in such experiments resulted from a combination of factors, any one of which may cause a decline in blood pressure. The experimental conditions may be analyzed as follows:

Let X symbolize the effects of hemorrhage and loss of fluid;
" Y " " " " anesthesia;
" Z " " " " absorption from damaged tissues.

Then shock, as indicated by a decline in the blood pressure, is represented by the formula:

$$X + Y + Z = \text{Shock}$$

Evaluation of an equation containing two or more unknown quantities is as illogical in medical science as in mathematics. It is absurd even to assume that those quantities will have the same relative values in any two experiments, for their nature is essentially

that of indeterminate variables. Under such conditions of experimentation the recorded phenomena may be due either to the narcotic, or to absorption, or to the associated hemorrhage, or in part to each. Yet, ignoring the effects of absorption and of anesthesia, the conclusion was drawn that the entire circulatory disturbance resulted from hemorrhage and loss of fluid locally.

It may be stated with emphasis that this combination of indeterminate variables is responsible for much confusion and lack of agreement in interpretations. This statement does not imply criticism of any author or group; it merely directs attention to serious defects and sources for error inherent in methods commonly used for experiments on shock.

The Pathologic Anatomy of Shock. Last but not least of the causes for divergent interpretations was failure to apply to the problem the methods used by pathologists. The belief had been accepted, apparently without question, that shock is purely a physiologic disturbance unaccompanied by significant morphologic changes. It was not realized that in this, as in other conditions of disease, valid interpretations find corroboration in the accompanying morphologic alterations.

My colleagues and I made a series of experiments for the dual purpose of testing the effects of products absorbed from damaged tissues and of studying the circulatory changes seen in the viscera after death by shock.

The Effects of Absorption. A method was devised to determine what effects would follow the absorption of substances derived from bruised or damaged tissues. Fresh, finely ground, muscle pulp introduced into the peritoneal cavity of normal dogs caused progressive circulatory deficiency having all the characteristics of shock.[22] These did not differ in any particular from the effects of extensive burns, histamine, peptone poisoning, or anaphylaxis. In such experiments, hemorrhage and narcosis were eliminated for no hemorrhage occurred and the brief ether anesthesia, given while opening the abdomen, had passed off hours before circulatory effects developed. Other tissues, as brain, liver or kidney, produced similar effects. Watery extracts of the tissues mentioned or of intestinal mucosa disturbed the circulation in a similar manner. By such methods it was possible to eliminate two complicating factors from the conditions of experimentation and to evaluate the effects of absorption alone. In each instance shock accompanied by hemoconcentration resulted from the absorption or the injection of the substance mentioned, uncomplicated by the effects of hemorrhage or of anesthesia.

Morphologic Evidence. The visceral appearances after death were indicative of endothelial relaxation in extensive visceral areas.[21a,23] Briefly summarized, these include capillo-venous congestion of the liver, kidneys, gastro-intestinal mucosæ, lungs, and of the serosæ.

Frequently there are petechial hemorrhages in these tissues, in the meninges and occasionally in the brain. When death is somewhat delayed, the soft tissues are edematous and there are effusions of fluid into the serous cavities. The visceral changes described had been noted many times[21c] in both experimental and clinical shock but without comment on their possible significance. These changes appear directly related to endothelial damage as described earlier in this discussion. They indicate the effects of agents or conditions which have altered seriously the structure and function of the capillaries.

Exactly similar pathologic alterations were seen in the viscera after death from $HgCl_2$ poisoning, eclampsia, intestinal strangulation, acute pancreatitis, burns and after infections of unusual severity. They were seen also after shock produced experimentally by a wide variety of agents. These findings indicate that circulatory disturbances, originating in the capillaries, may result from various types of injury but that in each instance the clinical, physiologic and pathologic features are identical in kind.

Several writers have attributed shock resulting from trauma or burns, to loss of plasma locally, as edema and blister fluid, about the injured areas. Such loss of fluid often is important as a contributory factor, but *local* permeability and transudation of fluid do not explain the *visceral* congestion and edema which accompany shock from tissue injury. The occurrence of such changes in areas remote from the injury indicates systemic, not local, effects. If a colloidal dye, such as trypan blue, is injected into the blood during the development of shock, areas of thoracic and abdominal tissues become stained diffusely with the dye. This indicates endothelial permeability in extensive regions, not limited to those about the injury.

A significant item of evidence, bearing on the underlying vascular dynamics, is the occurrence of edema of the lungs and other soft tissues after shock from diverse causes. This suggested that perhaps pulmonary edema might be produced experimentally by inducing shock of sublethal degree or in degrees not immediately fatal. Accordingly, experiments were devised to test this possibility.[23] Shock with delayed death, resulting from repeated subcutaneous injections of histamine, from burns, from injections of bile, from intestinal obstruction and from other conditions, caused marked pulmonary edema accompanied by hemoconcentration. This result corroborated the belief that endothelial permeability in extensive areas is a major factor in the mechanism involved (see Fig. 1).

Lungs whose circulation is impaired, and whose spaces are filled with albuminous fluid, present ideal conditions for the development of infection. A common type of hemorrhagic edematous pneumonia[21b] develops almost inevitably as a terminal event if neither death nor recovery from shock occurs soon.

Recent Theories. Two recent theories concerning the origin of shock are based upon the physiologic reactions by which systemic disturbances are compensated. These theories appear diametrically opposed, for one of them interprets shock as the *inadequacy* of the mechanism of compensation, while the other explains it as the result of *compensatory hyperactivity*.

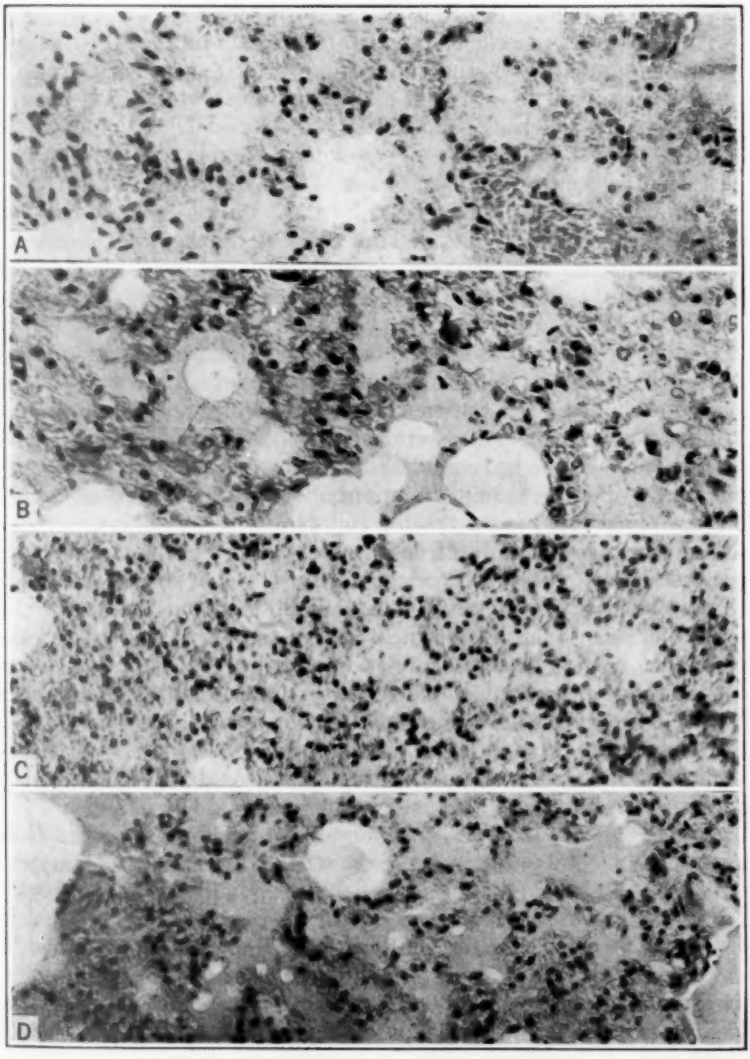

FIG. 1.—Experimental pulmonary edema. *A*, by subcutaneous injections of histamine; *B*, by scalding of the skin; *C*, by muscle pulp in the peritoneum; *D*, by intestinal strangulation.

The Alarm Reaction. Selye[27a,b] has called attention to a syndrome which appears when severe injury is inflicted upon the animal organism. This syndrome is independent of the nature of the damaging agent and represents a response to damage as such. Exposure to cold, traumatic injuries, excessive muscular exercise, spinal shock, anaphylaxis, acute infections and intoxications with various drugs will evoke this syndrome, which is interpreted as an expression of general defense.

The term *alarm reaction* is applied to the sum total of the biologic phenomena elicited by the sudden effects of damaging agents. It represents a "call to arms" of all the resources which tend toward adaptation or defense. Shock itself is defined as a condition of suddenly developing intense systemic (general) damage and is described as occurring in two phases, *shock* and *counter-shock*.

The first phase is characterized by the usual physiologic features and clinical signs of shock. This phase is interpreted as one of relative adrenal insufficiency. Death may follow if the degree of adaptability is limited, *i. e.*, if the defensive resources are inadequate to counteract the damage.

If the first phase does not end fatally, it is followed by the second phase, that of counter-shock, consisting of a reversal of most of the items mentioned and a return toward normal physiologic conditions.

This conception omits essential parts of the problem from consideration. Others have studied the mechanism by which damaging agents disturb normal functions; Selye has focussed attention on the physiologic resources for counteracting the damage. The former say the animal dies from the systemic effects of the damage; the latter attributes death to inadequacy of the defensive reactions. Obviously, interest should not be limited to the dynamics of the damaging agents but should include also the counteractive mechanisms. However, shock interpreted as inadequacy of the physiologic defenses presents an uncompleted picture. One still would inquire by what mechanism is the circulation disturbed and why are the metabolism, fluid balance, renal function and chemical concentrations altered. These important items in the syndrome of shock can hardly be interpreted as adaptive or defensive in character.

Hyperactivity of the Sympatho-adrenal System. It is known that injections of epinephrin in large amounts will cause the complete syndrome of shock (Bainbridge,[1] Erlanger,[8] Lamson[18] and others). The resulting vasoconstriction eventually leads to an oxygen deficit in the tissues with ensuing capillary dilatation and permeability of endothelium, thereby initiating a progressive circulatory deficiency. Freeman[10,11] believes that, in response to pain or emotions and to the injury itself, hyperactivity of the sympatho-adrenal system produces a similar effect. This is offered as an explanation for shock resulting from trauma, burns, hemorrhages and other causes.

A critical examination of the evidence reveals several points of

seeming incompatibility with known facts. Conditions accompanied by prolonged intolerable pain, such as renal or biliary colic, do not cause shock nor can it be produced experimentally by prolonged stimulation of nerve trunks. The sympatho-adrenal systems of men and animals are called into maximal activity during physical combat. Yet no instances of shock have been noted under these conditions, independent of serious wounds or hemorrhage.

Neither cutting the spinal cord nor severing all nerve paths from the traumatized area will prevent the development of shock. Animals previously subjected to bilateral sympathectomy (Freedlander and Lenhart[9]), also adrenalectomized animals (Swingle and associates[29a,b]), develop shock from trauma or from other causes as readily as do normal animals. Hyperactivity of the sympatho-adrenal system would appear to be eliminated in such experiments.

The immediate treatment of an extensive burn, as with tannic acid, will prevent shock or lessen its degree. It is not probable that such treatment reduces the sympatho-adrenal response to the tissue damage nor to the pain and fright of the accident.

Finally, it has been shown that deep Roentgen irradiation of the abdomen causes the complete syndrome of shock in dogs, accompanied by hemoconcentration and by distinctive visceral changes as described. Roentgen irradiation is an agent which, like heat, causes tissue injury. It is followed by delayed necrosis of the glandular epithelium in the intestinal mucosa and the development of shock is delayed correspondingly. Warren and Whipple[31] believed that absorption of products from the tissues damaged by Roentgen rays resulted in progressive deficiency of the circulation, and recent investigations[24] have supported that view. Irradiation is painless and whatever emotional responses it might cause would subside shortly. The dogs appeared entirely normal on the following day. No anesthesia was used, nor was there hemorrhage nor local loss of fluid. Such conditions provide no apparent cause for the development of sympatho-adrenal hyperactivity several days later.

The chief experimental evidence supporting this theory was derived from a comparison of the effects of hemorrhages and transfusions in two groups of dogs. For reasons not entirely clear, the normal dogs were subjected to far greater losses of blood than the sympathectomized ones. The authors concluded that the latter were more resistant to the effects of hemorrhage. Since shock and the effects of hemorrhage are not identical (*vide supra*), these experiments may not bear directly upon the problem. If the authors have tested the effects of trauma or of other shock-producing agents upon sympathectomized dogs, the results have not been published.

It appears that more definite evidence will be required before hyperactivity of the sympatho-adrenal system can be considered seriously as a major factor in the mechanism of shock.

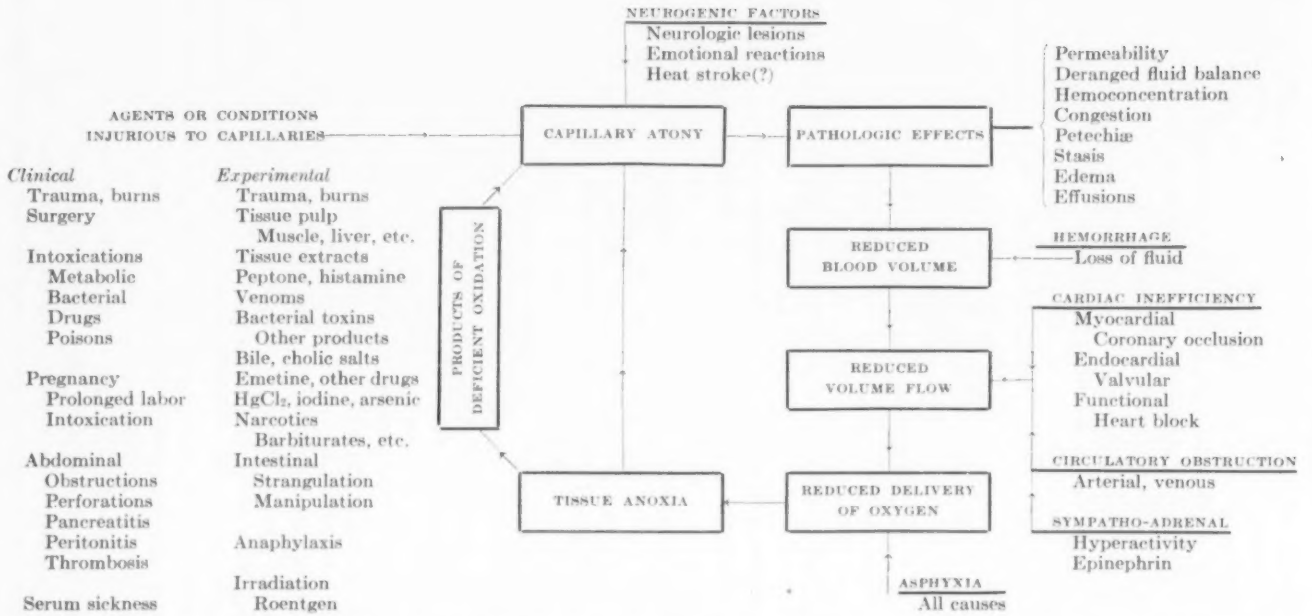

DIAGRAM 3.—The relationship of various factors in the pathologic physiology of shock. The reciprocal effects of *capillary atony* and *tissue anoxia* give this mechanism the self-perpetuating quality of a vicious circle.

Summary. An analysis of the sources for disagreement concerning the dynamics of shock indicates that four major causes have operated to confuse interpretations of its phenomena and of their interrelationships.

The first of these was deficient knowledge of capillary reactions and of circulatory disturbances originating in them. A comprehension of these has contributed immeasurably to an understanding of shock resulting from trauma, burns and other types of tissue damage. It clarifies also the disturbances of fluid balance and of chemical concentrations which are associated regularly with this condition.

Failure to distinguish between shock and hemorrhage has caused much confusion. Hemorrhage, when present, is a potent contributory factor, but the effects of uncomplicated hemorrhages present numerous features opposite in character from those which constitute the syndrome of shock.

Variations in blood pressure used as a criterion, and failure to consider the depressor effects of both anesthesia and losses of blood, have led to undependable conclusions concerning the effects of absorption. Varied forms of experimentation have shown that products derived from normal tissues, independent of narcosis and hemorrhage, will produce the syndrome of shock accompanied by its characteristic physiologic and morphologic features.

Hemoconcentration during life, and the presence of engorged capillaries, stasis, petechiæ and edema after death, indicate endothelial damage as a major factor. The occurrence of these conditions in extensive visceral areas remote from the injury indicates systemic, not local, endothelial damage. Shock, like other conditions of disease, is accompanied by a pattern of morphologic changes which are related etiologically to its mechanism of origin and which corroborate the interpretation of shock as due to endothelial damage.

The major causes for disagreement concerning shock have been discussed. In view of the character and magnitude of these, it is not strange that final clarification of the problem has been delayed. When these causes have been recognized and obviated, it becomes a simple matter to assemble the related facts into an intelligible picture. This diagram presents that picture as we see it.

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OBSERVATIONS ON THE ETIOLOGIC RELATIONSHIP OF ACHYLIA GASTRICA TO PERNICIOUS ANEMIA.

IX. Difference in Site of Secretion of Intrinsic Factor in the Hog and in the Human Stomach.*

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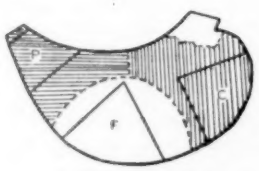
In previous observations[1,2] it has been demonstrated that the fasting normal human gastric juice contains a principle (intrinsic factor) which, when administered with beef muscle (extrinsic factor) to patients with Addisonian pernicious anemia, causes increased blood production and clinical improvement. Because neither human saliva nor pure duodenal secretion was effective upon admixture with beef muscle,[4] it was tacitly assumed that the so-called intrinsic factor was secreted in man by that portion of the stomach which in pernicious anemia exhibits atrophy or disappearance of the normal glandular structure.[5a,b,8,9b] Except by inference from the work

* The expenses of this investigation were defrayed in part by the J. K. Lilly Gift to the Harvard Medical School.

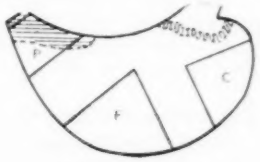
with hog stomach preparations carried out by Meulengracht,[9a,c] Ungley[18] and others, and from experimental gastrectomies in animals, no physiologic evidence on the localization of the source of intrinsic factor in the normal human stomach is available.

The technique utilized by Meulengracht was to test in patients with pernicious anemia the blood-forming activity of desiccated preparations of hog stomach after division into cardia, fundus and pylorus portions, respectively. Meulengracht[9a,b,10] deduced from such observations and from studies of the comparative histology of the hog and human stomachs that the "pyloric gland organ" in both species is the principal site of secretion of intrinsic factor. This conclusion involves, however, two fundamental assumptions: 1, that the presence in desiccated hog stomach preparations of material possessing blood-forming activity in pernicious anemia defines the site of secretion of intrinsic factor; and 2, that such observations with the hog stomach are directly applicable to man. The purpose of the present investigation was to determine the validity of these two assumptions; especially because, as both Meulengracht[9b] and Magnus and Ungley[8] have recently pointed out, the degenerative process in the stomach in pernicious anemia does not significantly involve the "pyloric gland organ," inferred by Meulengracht to be the chief source of intrinsic factor in man.



(A) HOG STOMACH

FIG. 1A



(B) HUMAN STOMACH

FIG. 1B

FIG. 1A.—Distribution of pylorus, cardia and fundus type of glands in hog stomach (shaded areas *P* and *C* and clear area *F*) according to Meulengracht and Ohlsen.[10] Solid lines indicate plan of incisions for pylorus, cardia and fundus preparations of hog stomachs according to Meulengracht and Schiødt[11] and as employed in the present observations for pylorus and fundus preparations of hog stomachs.

FIG. 1B.—Distribution of pylorus (horizontal shading), cardia (vertical shading) and fundus (clear area) type of glands in human stomachs according to Paschkis and Orator.[12] Plan of incisions (solid lines) employed for pylorus, cardia and fundus preparations of human stomachs was identical with that employed for hog stomachs.[11]

General Methods. Various preparations of hog and human stomachs were secured in the following manner, except as indicated in the description of certain individual observations. The stomachs of freshly killed hogs were collected and divided into those portions defined by Meulengracht[9b] as fundus and pylorus, as shown in Figure 1*A*. After removal of adherent fat and brief washing with cold water, the wet weight of each pylorus portion averaged about 60 gm. and that of each fundus portion about 100 gm. An appropriate number of specimens of each portion were then finely ground and spread on shallow pans for desiccation in a current of air at room temperature. In certain observations indicated below, the mucosa

was removed and ground with beef muscle. After from 24 to 48 hours the film of dried material was scraped from the pan and ground in a mill. It was then carefully defatted with ether, further pulverized and placed in a desiccator over soda lime for final drying. Thereafter the dry, powdered material was stored in glass-stoppered bottles out of the light, until required for use.

Human stomachs were removed at postmortem examination, usually within 12 hours and always within 24 hours after death. The subjects providing this material were all adults, of both sexes and of various ages, who had died suddenly of cardiac or cerebral lesions and in whom there was no clinical or postmortem evidence of infection of any type. Immediately after removal, the stomachs were freed of adherent fatty tissue and divided arbitrarily into the three portions defined by Meulengracht for the hog stomach, as shown in Figure 1*A*. The average wet weights of the three portions of the stomach were: pylorus 20 gm., fundus 23 gm., cardia 18 gm. Appropriate numbers of specimens of each portion were then briefly rinsed in cold running tap water and ground with an equal weight of beef muscle. Thereafter the material derived from each portion was desiccated, defatted and stored as described above. When finally ready for use, all the preparations were odorless, homogeneous, grayish-white powders weighing approximately one-fourth the wet weights of the original tissues.

The blood-forming activity of these preparations in pernicious anemia was determined by the effect of their daily administration to suitable patients, especially by the presence or absence of significant reticulocyte responses, the interpretation of which has previously been fully described.[12] Unless otherwise indicated, 10 gm. of each preparation was given 3 times daily for 10 days; and if the material under test produced no response, the ability of the patient to react was determined in an immediately subsequent period by the administration of an active experimental preparation or of 10 gm. of Ventriculin (N.N.R.) 3 times daily for 10 days. The methods of dietary control and of reticulocyte and red blood cell counting have been described in detail in previous publications.[1,2,4]

The Blood-Forming Activity of Desiccated Preparations of Various Portions of the Hog Stomach as an Indicator of the Site of Secretion of Intrinsic Factor. The correctness of the assumption that the blood-forming activity of desiccated hog stomach is due to the presence of the so-called intrinsic factor is suggested by the following observations: 1, the active principle of hog stomach, like that of normal human gastric juice, is relatively thermolabile, each being destroyed by boiling for 5 minutes or by incubation at from pH 2.5 to 3.5 for 48 hours;[1,4] 2, boiled hog stomach mucosa, itself ineffective, becomes capable of blood formation in pernicious anemia after admixture with normal human gastric juice.[1] Nevertheless, the fact that the combined work of Sharp,[16] Meulengracht,[9a,c,d] Thompson,[17] Uotila,[19] Ungley,[18] Schemensky[14] and others indicates that preparations of every portion of the alimentary tract of the hog, *with the exception of the fundus of the stomach*, are effective in causing increased blood production in pernicious anemia raises the question whether the experimental techniques employed by Meulengracht[9a,c,d] and Ungley[18] could be, in any way, responsible for their failure to obtain activity with fundus preparations. Thus, it is conceivable that the apparent ineffectiveness of the fundus might have been due to

local destruction of intrinsic factor, to failure of the fasting animal to secrete sufficient intrinsic factor, to the presence of intrinsic factor in a zymogen form or to the necessity, after secretion, of its activation of or by substances contributed by the pylorus region of the stomach. These theoretical possibilities were accordingly investigated.

The first undertaking was to determine whether the method employed for desiccation and defatting was capable of preserving the well-established anti-anemic activity of a hog stomach pylorus preparation. Positive evidence for this was obtained by the administration of 30 gm. of a desiccated, defatted mixture of equal wet weights of hog stomach pylorus mucosa and of beef muscle daily for 10 days. As shown in Table 1, Case 81, there was a significant effect on blood production during this period.

Meulengracht's and Ungley's observation that the feeding of desiccated hog fundus preparations does not cause increased blood production in pernicious anemia was confirmed by the negative results of the daily administration of 30 gm. of desiccated hog fundus during the first period of observation of Case 82, who responded satisfactorily to the administration of Ventriculin (N.N.R.) during a third period of observation. In the second period the possibility was investigated that the presence of hydrochloric acid and pepsin in the fundus during the process of desiccation might have been responsible, in Meulengracht's experiments, for the destruction of intrinsic factor and consequently for the absence of anti-anemic activity. Indeed, Meulengracht and Schiødt[11] have shown that the fundus of the hog stomach is the chief source of pepsin and is the only portion of the stomach in which stimulation of secretion by histamine injection causes an acid reaction to Congo red paper. Moreover, it has been demonstrated[4] that the incubation at 37.5° C. of hog stomach mucosa at from pH 2.5 to 3.5 for 48 hours completely destroys its blood-forming activity. And, finally, it has been shown that intrinsic factor is partially destroyed by incubation of normal human gastric juice at pH 1.5 for 2 hours,[1] but is not affected by such treatment at pH 10.[6] Accordingly, in order to afford to any intrinsic factor present the maximum protection against acid or against enzymes active at an acid reaction, the fundus portion of the hog stomach was removed immediately and was finely ground with an equal weight of water. To this was added about 4 cc. of normal sodium hydroxide per 100 gm. of fundus, which was found to be a sufficient amount to produce a reaction of pH 7.2. Nevertheless, as shown in Table 1, this neutralized fundus preparation, like the unneutralized preparation, produced no detectable effect on blood formation in Case 82, although in a third period of observation* the patient responded to the daily administration of 30 gm.

* Not shown in Table 1 because of lack of space.

TABLE 1.—EFFECT OF DAILY ORAL ADMINISTRATION IN PERNICIOUS ANEMIA OF VARIOUS DESICCATED AND DEFATTED HOG STOMACH PREPARATIONS.
(Dosage = 30 gm. daily, unless otherwise indicated.)

Days of treatment.	Case 81.		Case 82.		Case 83.		Case 84.		Case 85.		Case 86.		Case 90.	
	R.B.C., mills.	Retics., %.	R.B.C., mills.	Retics., %.	R.B.C., mills.	Retics., %.	R.B.C., mills.	Retics., %.	R.B.C., mills.	Retics., %.	R.B.C., mills.	Retics., %.	R.B.C., mills.	Retics., %.
First Periods.														
	Pylorus mucosa and beef muscle.		Fundus.		Neutralized fundus (obtained after food and histamine injection).		Acidified fundus and beef muscle.		Pylorus mucosa 10 gm. and beef muscle 100 gm. (28 gm. = dry weight).				Fundus after standing for 24 hours.	
0	1.39	2.4	1.40	1.6	1.63	0.4	1.12	2.2	1.90	2.0	1.50	2.0	2.20	3.4
2	1.32	2.0	1.22	0.8	1.58	1.0	0.98	2.0	2.30	2.0	1.57	1.0	1.91	1.2
4	1.06	4.6	1.27	0.6	1.59	0.6	1.12	1.2	2.18	3.0	1.77	1.8	1.79	0.4
6	1.07	7.8	1.27	2.2	1.63	1.0	1.02	0.2	2.41	3.2	1.91	0.8	2.05	0.4
8	1.24	14.8	1.24	3.1	1.54	1.0	0.97	0.6	2.25	**10.4**	1.95	8.8	2.17	0.1
10	1.34	**20.6**	1.20	2.2	1.48	0.8	0.94	1.0	2.47	8.8	2.45	**9.0**	1.74	1.0
12	1.43	17.4							2.66	4.0	2.56	5.0		
14	1.42	13.2							2.93	2.4				
Second Periods.														
			Neutralized fundus.		Ventriculin (N.N.R.).		Ventriculin (N.N.R.).				Pylorus mucosa 10 gm., fundus 60 gm., beef muscle 50 gm. (28 gm. = dry weight).		Pylorus after standing for 24 hours.	
2			1.18	2.8	1.65	0.6	0.99	0.4			2.63	5.0	2.14	0.2
4			1.13	0.2	1.57	1.0	1.06	1.4			2.84	4.0	2.13	2.2
6			1.02	2.0	1.59	1.8	1.20	4.2			2.64	2.2	2.32	4.8
8			0.95	2.2	1.44	6.6	1.26	**14.4**			2.62	1.8	2.25	**7.8**
10			1.37	2.8*	1.53	**9.8**	1.46	11.4			2.89	1.6	2.68	3.6
12						6.8	1.60	3.6			2.91	1.0	2.57	2.6
14					2.21	5.0	1.46	3.6			2.94	1.4		

* A subsequent 21% reticulocyte response to Ventriculin (N.N.R.) on the 10th day of a third period is not shown.

of Ventriculin (N.N.R.). For example, on the 10th day the reticulocytes reached a peak value of 21%.

Because Meulengracht did not state whether the fundus preparations utilized in his work were obtained from fasting hogs or from hogs which had previously been fed, the possibility that his negative results with fundus were due to an inadequate stimulus to secretion of intrinsic factor was investigated in the following manner. Approximately 1½ hours before slaughtering, hogs were fed a mixture of milk and cornmeal, and about 1 hour later each was given an intramuscular injection of 3 mg. of histamine hydrochloride. As soon as the fundus portion of the stomach had been dissected, it was finely ground in an equal weight of cold water and the reaction adjusted to pH 7.2 with about 4 cc. of normal sodium hydroxide per 100 gm. of fundus. Thereafter, the material was desiccated and defatted as usual. As shown in Table 1, Case 83, during the first period of observation the daily administration of 30 gm. of this desiccated preparation was quite ineffective, whereas in the second period the daily administration of 30 gm. of Ventriculin (N.N.R.) caused a moderate reticulocyte response.

The next possibility investigated was that intrinsic factor might become active only after secretion into an acid medium such as exists in gastric juice; that is, just as for the activation of pepsin from its zymogen form, hydrochloric acid might be essential for the activation of intrinsic factor. It is true that this appeared to be unlikely because of previous demonstrations[3,7] of intrinsic factor in gastric juice containing no free hydrochloric acid. Nevertheless, to fresh preparations of hog stomach fundus was added an equal weight of water and sufficient strong hydrochloric acid to effect a reaction of about pH 2 after thorough grinding of the material. The acidified fundus pulp was allowed to stand in the icebox for 1 hour. It was then ground with an equal weight of beef muscle, and the reaction of the mixture brought to approximately pH 6.5 with strong sodium hydroxide. Thereafter the material was desiccated, defatted and fed to Case 84 in a dosage of 30 gm. daily during the first period of observation. As shown in Table 1, it produced no significant effect on blood formation, although in the second period of observation the daily administration of 30 gm. of Ventriculin (N.N.R.) was distinctly effective.

In his most recent publication on this subject, Meulengracht[9b] considers the possibility that the fundus portion of the normal stomach might supply a hormonal "pacemaker" for the production of intrinsic factor by the pylorus region. Another hypothesis consistent with his observations is that intrinsic factor, though secreted by the fundus, might become active only upon contact with the pylorus mucosa, or with some secretion of that portion of the stomach. Accordingly, this possibility was examined. As shown in Table 1, in the first period of observation of Case 85 the daily

administration of 28 gm. of a desiccated preparation derived from a mixture of 10 gm. of fresh pylorus mucosa and 100 gm. of beef muscle had a powerful effect on blood production. In Case 86 the possibility of potentiation of fundus by admixture with pylorus mucosa was tested. In the first period of observation, the effectiveness of the daily administration of 28 gm. of desiccated material derived from 10 gm. of pylorus mucosa and 100 gm. of beef muscle was confirmed. In the second period, 28 gm. of a desiccated preparation derived from 10 gm. of pylorus mucosa, 60 gm. of whole fundus and 50 gm. of beef muscle, administered daily, was not shown to possess greater hematopoietic activity.

Thus, attempts at securing evidence of the presence of intrinsic factor in hog stomach fundus preparations by neutralization, by stimulation of secretion, by preliminary acidification before neutralization and by admixture with pylorus tissue all failed. These observations appear completely to confirm the experiments of Meulengracht, Ungley and others purporting to show that whereas desiccated preparations of the fundus of the hog stomach have no effect on blood production in pernicious anemia, similar preparations of the pylorus region are highly active. Their assumption that the distribution of such blood-forming activity is an indication of the site of secretion of intrinsic factor in the hog stomach is thus entirely supported by the present observations.

Difference in Site of Secretion of Intrinsic Factor in the Hog and in the Human Stomach. Meulengracht[9b] and Magnus and Ungley[8] have pointed out the apparent conflict between the existing physiologic and histologic evidence on the site of secretion of intrinsic factor in the human stomach. Thus, their feeding experiments[9a,c,18] with desiccated hog stomach preparations indicate that the fundus of the hog stomach does not contain intrinsic factor, whereas their careful histologic studies[8,9b] in pernicious anemia confirm the fact, observed by others,[5a,b] that in this condition the fundus of the human stomach is the region of degeneration. Meulengracht's experiments demonstrating the hematopoietic activity of both desiccated hog stomach pylorus and duodenum led him to infer that the "pyloric gland organ," regarded as including the region of Brunner's glands of the duodenum and the histologically similar pyloric glands, is likewise in man a source of intrinsic factor. This conclusion is, however, in conflict with the normal histologic appearance of the pylorus and duodenum in pernicious anemia[8,9b] and with physiologic evidence from observations on man. Thus, it has been demonstrated[4] that although normal human duodenal contents which include gastric juice contain intrinsic factor, when gastric secretion is excluded from the duodenum intrinsic factor is no longer present in the secretion collected therefrom. It therefore appeared to be possible that these discrepancies might depend upon a species

difference between man and the hog as to the site of secretion of intrinsic factor.

Accordingly, the blood-forming activity in pernicious anemia of desiccated preparations of the human stomach was determined after arbitrary division into three portions, "pylorus," "fundus" and "cardia," respectively, according to Meulengracht's plan for the hog stomach, which is shown in Figure 1*A*. The fact that the nomenclature applied to these divisions of the human stomach does not, as in the hog stomach, correspond with areas of different gland structure was clearly recognized and will be discussed below. To each freshly excised and washed portion of the stomach was added an equal weight of beef muscle. The details of the subsequent desiccation, defatting and storage of the preparations have been described above. As shown in Table 2, Case 87, the daily administration of 30 gm. of the pylorus preparation during the first period of 10 days caused a slight reticulocyte response. There was no clinical improvement. No significant increase in red blood cells occurred until during the second period when, as a result of the daily administration of 30 gm. of Ventriculin (N.N.R.) for 10 days, there was a significantly greater reticulocyte response and marked clinical improvement. In the first periods of observation of Cases 88 and 89, when 30 gm. of a fundus preparation and of a cardia preparation, respectively, was administered daily for 10 days, striking reticulocyte responses and clinical improvement occurred. During the second periods, the daily feeding of 30 gm. of Ventriculin (N.N.R.) to each case resulted in no detectable second rise of reticulocytes.

TABLE 2.—EFFECT OF DAILY ORAL ADMINISTRATION IN PERNICIOUS ANEMIA OF DESICCATED AND DEFATTED HUMAN STOMACH PREPARATIONS.

(Dosage = 30 gm. daily.)

Days of treatment.	Case 87. R.B.C., mills.	Case 87. Retics., %.	Case 88. R.B.C., mills.	Case 88. Retics., %.	Case 89. R.B.C., mills.	Case 89. Retics., %.
	First Periods: Human Stomach Preparations.					
	Pylorus preparation.		Fundus preparation.		Cardia preparation.	
0	1.62	1.8	1.80	0.8	1.44	1.8
2	1.69	0.8	1.59	0.9	1.42	2.0
4	1.44	0.4	1.68	5.0	1.37	3.1
6	1.46	1.0	1.69	19.2	1.57	11.6
8	1.47	2.0	1.86	**25.3**	1.64	**27.8**
10	1.54	**6.4**	2.14	16.2	1.99	18.6
	Second Periods: Hog Stomach Preparation (Ventriculin N.N.R.).					
	Ventriculin.		Ventriculin.		Ventriculin.	
2	1.55	4.9	2.57	2.8	2.18	16.6
4	1.50	3.4	2.67	3.9	2.12	6.8
6	1.49	8.9	2.79	1.0	2.34	4.4
8	1.60	8.1	2.58	0.8	2.11	4.6
10	1.51	10.8	2.74	1.2	2.04	4.3
12	1.85	**18.8**	2.60	1.2	2.42	3.4
14	2.39	16.5				

A possible criticism of these observations is that whereas the hog stomachs were obtained immediately after the death of the animals, the human stomachs were secured usually within 12 hours but sometimes between 12 and 24 hours after death. Accordingly, although these postmortem conditions did not destroy the potency of the human material, the question arises whether the distribution of activity might have been modified by prolonged contact postmortem of one portion of the stomach with secretion from another. As a control on such postmortem effects in the human material, preparations were made from hog stomachs previously subjected to the following procedure. Immediately after removal from the hogs, the pyloric and esophageal orifices of the stomachs were occluded with a tightly tied ligature. The unopened stomachs were allowed to stand at room temperature for 6 hours and were then placed in the icebox for an additional 18 hours. Thereafter the stomachs were opened, the food and gastric secretions were removed, and specimens of the pylorus and fundus were excised, washed, desiccated and defatted in the usual manner. In the first period of observation of Case 90, shown in Table 1, the daily administration of 30 gm. of the fundus preparation was found to be without effect, but in the second period the pylorus preparation caused increased blood production. Thus, despite contact with gastric contents for 24 hours after death, the fundus preparation of the hog stomach remained hematopoietically ineffective. By analogy, therefore, it seems proper to assume that the distribution of the activity of the human stomachs was not modified by postmortem effects.

Discussion. According to these observations, the blood-forming activity of desiccated preparations of the human stomach after arbitrary division into areas resembling the pylorus, fundus and cardia portions of the hog stomach, as defined by Meulengracht, had a distinctly different distribution from that obtaining in similar areas of the hog stomach. Thus, the so-called fundus and cardia preparations of the human stomach were highly effective, whereas the pylorus was, at best, weakly active compared with Ventriculin (N.N.R.) in the dosage specified. The observations reported in the first portion of this paper lend weight to the validity of Meulengracht's assumption that the distribution of the anti-anemic potency is an indication of the site of secretion of intrinsic factor in the stomach of the hog. Application of the same assumption to the present results with desiccated human stomach preparations leads to the conclusion that in man the areas here arbitrarily designated as "fundus" and "cardia," but not the "pylorus" region of the stomach, are the important sites of the formation or secretion of intrinsic factor. If reference is made to the histologic studies of the human stomach by Paschkis and Orator,[13] the type of glandular structure presumably present in each of these areas may be determined. According to these authors, the pyloric glands in the

human stomach are found in an area extending along the lesser curvature to the angulus, or about 6 cm. from the pylorus, but along the greater curvature run only a very short distance from the pylorus. The cardiac glands are confined to an area a few millimeters in width adjacent to the border of the esophageal mucosa. The fundic glands occupy the rest of the stomach wall. Reference to the approximate outlines of these areas shown in Figure 1*B* indicates that the so-called pylorus preparation of the human stomach may have contained a considerable proportion of fundic glands, whereas the so-called fundus and cardia preparations contained fundic glands only. There is, thus, no question but that in these human stomachs the fundus type of gland was associated with anti-anemic activity. Indeed, the weakly positive effect observed with the so-called pylorus preparation might also be ascribed to the presence of fundic glands.

According to this evidence, then, the site of secretion of intrinsic factor, as defined by the hematopoietic activity of desiccated human stomach preparations, is found to correspond to the site of the degenerative process[5a,b,g,9b] in the stomach in Addisonian pernicious anemia, a disease in which it is clear that intrinsic factor is deficient. The present observations, suggesting the relative insignificance of the "pyloric gland organ" as a source of intrinsic factor in man, are in agreement with the previous observation[4] that pure duodenal secretion in man does not contain detectable amounts of intrinsic factor. Thus, with the exception of the recent report of Schenken, Stasney and Hall,[15] all the observations which have been made on man point to the fundic gland area of the human stomach as the important source of intrinsic factor. The evidence becomes contradictory only when conclusions which undoubtedly obtain for the hog are directly translated to man.

Conclusions. 1. By means of observations under controlled conditions on patients with Addisonian pernicious anemia, the previous experiments of Meulengracht, Ungley and others concerning the effectiveness of desiccated preparations of the pylorus and the ineffectiveness of similar preparations of the fundus of the hog stomach were confirmed.

2. It was not possible to develop an active fundus preparation of hog stomach by measures designed: *a*, to prevent the local destruction of intrinsic factor; *b*, to increase its secretion; *c*, to activate a zymogen form; or *d*, to potentiate intrinsic factor by contact with substances in the pylorus region of the stomach.

3. These facts contribute support to Meulengracht's assumption that the anti-anemic potency of the pylorus region of the hog stomach indicates it as a site of secretion of intrinsic factor in that animal.

4. Application of this assumption, however, to the present observations with desiccated preparations of normal human stomach

suggests the conclusion that in man those areas containing the fundus type of gland, and not the "pyloric gland organ," are the important sites of secretion of intrinsic factor.

5. The present observations suggest that the source of intrinsic factor in the normal human stomach coincides with the site of the degenerative process seen in histologic preparations of the stomach in pernicious anemia.

6. Because the cardia of the human stomach is apparently an active site of secretion of intrinsic factor, gastric resections in man which preserve this portion of the stomach should, theoretically, provide a source of intrinsic factor for the patient.

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RELATIONSHIP BETWEEN THE SPLEEN AND THE MORPHOLOGIC PICTURE OF BLOOD REGENERATION.

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Present concepts of blood physiology attribute but little of essential importance to the function of the spleen. As far as the main splenic functions—lymphocyte production and destruction of old erythrocytes—are concerned, other organs of the body economy can replace the spleen adequately. The rôle of the spleen as a

reservoir is not of primary importance and only in some occasional occurrence can it have vital significance. Hormonal and anti-infectious properties of the spleen have been emphasized by some authors, but conclusive proof of their rôle has not yet been obtained.

It is very well known that any blood regeneration is characterized by a peculiar morphologic picture showing the launching of young red blood cells (reticulocytes) into the circulation. The main morphologic feature is the presence of a reticulum within the vitally stained new cells; when stained by Giemsa or Wright stain, these cells are polychromatophilic. These two staining methods reveal also the erythrocytes with nuclear structures as the normoblast and the erythrocyte with nuclear particles.

Very few papers concern themselves with experimental work that includes the complete morphology of blood regeneration. Only the reticulocytes have been carefully observed in human anemias and in experimental animals. In the earlier studies of the blood much attention was paid to the normoblasts and erythrocytes with nuclear bodies because they were the only morphologic signs of blood regeneration, but careful experimental studies have not been made. Drinker, Drinker and Kreutzmann[2] pointed out that a true normoblastic crisis in the peripheral blood of dogs occurs after hemorrhage just before the rapid increase in the erythrocyte count and usually towards the end of the first week following the hemorrhage. These authors observed only once a crisis of 8000 normoblasts per c.mm., 12 days after the last bleeding. Crises of 5600 (5 days after bleeding), 4000 (4 days after) and 3000 (9 days after) are reported together with other minor crises. Muller[4a,b] observed normoblastic crises in rabbits after intravenous injections of India ink or gum shellac. With India ink the highest normoblast count found was 77,000 per c.mm., and counts above 20,000 per c.mm. were very often observed; with gum shellac the highest count was 80,000 per c.mm. and counts above 20,000 per c.mm. were easily verified. More recently Hamre and Miller[3] produced anemia by deficient iron intakes in two different groups of rats—non-splenectomized and splenectomized. They then observed during blood regeneration following iron and copper administration, a normoblastic crisis in both groups, much higher in the splenectomized group. The greatest crisis occurred 2 days after the metal administration gave a count of 5000 normoblasts per c.mm. in the non-splenectomized group. The splenectomized group after the same 2 days indicated a rise to 33,000 normoblasts per c.mm. with a secondary rise of 10,000 per c.mm. on the sixth day.

The present paper deals with studies concerning the morphology of the blood during regeneration following anemia produced by hemorrhage or by acetylphenylhydrazine injections, in normal and splenectomized dogs.

Methods. Detailed observations were made in 6 non-splenectomized and 3 splenectomized dogs. The splenectomized dogs were observed at different time intervals following the splenectomy (Dog 40–115 was studied 2 months after the operation; Dog 39–194, 11 months after, and Dog 24–70, 2½ years after). Further observations were made also in 13 dogs belonging to the anemia colony. Different levels of anemia were produced by hemorrhage with the usual jugular puncture method or by subcutaneous injections of acetylphenylhydrazine, dissolved in hot saline solution (10 to 20 cc.) just prior to injection. Daily observations of the blood picture were made in 11 periods during blood regeneration. Red blood cell counts were made in the usual manner with Thoma micro-pipette and Neubauer counting chamber. Hemoglobin was determined by the oxyhemoglobin method in the Klett-Summerson photoelectric colorimeter. Reticulocytes were counted by direct microscopic observation of a drop of blood mixed with a drop of 1% solution of cresyl blue in saline solution. The normoblasts (orthochromatic erythroblasts of Ferrata) were counted in relation to number of erythrocytes in smears stained with Giemsa stain; the young erythroblasts (basophilic erythroblasts of Ferrata) were counted in the same manner. For comparative purposes a case of thalassemia (Cooley's anemia) was studied, since it is well known that this type of human anemia is characterized by large numbers of normoblasts in peripheral blood.

TABLE 1.—ACETYLPHENYLHYDRAZINE ANEMIA.

	Red blood cells (mil. per c.mm.).					Hemoglobin (gm. per 100 cc.).				
	Splenectomized dogs.		Non-splenectomized dogs.			Splenectomized dogs.		Non-splenectomized dogs.		
Days of observation.	39–194	40–115	40–213	39–137	39–299	39–194	40–115	40–213	39–137	39–299
1	*5.4	*5.6	*5.8	‡5.5	*7.3	12.0	12.7	12.9	13.5	9.9
2	* ..	* ..	*4.8	‡4.9	*6.5	8.2	..	9.6	11.5	8.4
3	*4.0	*5.1	*4.6	‡4.0	*6.0	7.5	10.7	9.5	8.5	6.7
4	*3.6	* ..	* ..	3.0	* ..	5.8	..	..	6.1	
5	*2.8	*4.0	*3.0	2.0	3.1	..	7.9	5.6	4.4	3.9
6	* ..	3.6	*2.4	1.6	1.6	3.7	6.4	4.5	3.5	3.3
7	2.2	..	2.0	1.5	2.1	3.1	..	3.3	3.7	4.2
8	1.7	1.6	1.6	1.7	2.3	3.4	3.0	2.9	4.2	4.9
9	1.8	1.6	1.4	2.1	2.8	3.5	3.2	2.3	5.3	5.6
10	1.7	1.3	1.5	2.8	3.4	3.8	2.9	2.7	7.3	7.4
11	1.7	1.4	1.7	..	..	3.9	3.1	3.3		
12	1.7	1.7	2.0	3.3	..	..	3.5	4.1	7.9	
13	..	1.8	2.7	3.7	..	5.6	..	5.8	9.4	
14	2.4									
15	..	..	3.1	..	..	..	..	7.3		
16	..	..	3.7	..	..	7.3		8.3		
17	3.0	2.4	4.3	..	..	..	5.7	9.5		
18										

Dog 39–194—first day of observation is 11 months after splenectomy. Dog 40–115—2 months after splenectomy.

* Acetylphenylhydrazine, 300 mg. † Acetylphenylhydrazine, 200 mg. ‡ Acetylphenylhydrazine, 100 mg.

Observations and Discussion. Tables 1 and 1*a* present the results found in the acetylphenylhydrazine anemia. Table 1 shows that the lowest anemia levels are about the same in both groups of dogs, around 1,500,000 erythrocytes per c.mm., and 3 gm. hemoglobin in 100 cc. of blood. This is a very low level and all dogs became acutely sick for 2 or 3 days. The recovery from the anemia is always complete and very fast in both groups of dogs, showing that the spleen does not have any direct and indispensable function relating to the regeneration of this type of anemia. This same fact was observed by Robscheit-Robbins and Whipple[6] during the

recovery of experimental hemorrhage anemia in dogs. Table 1*a* shows that the reticulocytosis is about the same in both cases, the highest number was 79% in the splenectomized group (Dog 39–194), and 77% in the normal one (Dog 40–213). A sharp difference between the two groups is found in the number of normoblasts and basophilic erythroblasts. In the non-splenectomized dogs the highest normoblast count was 6000 per c.mm. (Dog 40–213), whereas in the splenectomized group was observed 25,000 per c.mm. (Dog. 39–194) and 22,000 (Dog 40–115), with 6 other figures above 10,000 per c.mm. The highest basophilic erythroblast count in the normal group was 700 per c.mm. (Dog 39–299), 16% when calculated in proportion to the normoblasts. The splenectomized group, on the other hand, demonstrated the highest count of 4300 per c.mm. which is 43% as related to the normoblasts. The peak of the normoblast crisis appears when the red blood cell begins to rise, and the basophilic erythroblast crisis follows 2 or 3 days thereafter when the normoblasts are going down. Those smears with 43% of basophilic erythroblasts are very interesting in this respect, and resemble the morphologic picture of severe human pernicious anemia during megaloblastic crisis.

TABLE 1A.—IMMATURE CELLS IN ACETYLPHENYLHYDRAZINE ANEMIA.

	Reticulocytes (%).					Normoblasts (thous. per c.mm.).					Ratio basophilic erythroblasts to normoblasts (%).				
	Splenectomized dogs.		Non-splenectomized dogs.			Splenectomized dogs.		Non-splenectomized dogs.			Splenectomized dogs.		Non-splenectomized dogs.		
Days of observation.	39–194	40–115	40–213	39–137	39–299	39–194	40–115	40–213	39–137	39–299	39–194	40–115	40–213	39–137	39–299
1	2	0.2	5	0.5	0.5	0	0	0	0	0	0	0	0	0	0
2	..	..	3	1	0.5	..	..	0	0	0	..	..	0	0	0
3	3	0.5	4	2	..	0	0	0	0	..	0	0	0	0	
4	5	..	..	3	2	0	..	..	0	1.8	0	..	..	0	
5	24	2	18	13	0	0.1	0	1.4	0.3	..	..	0	..	3	
6	32	3	17	25	10	4.2	0.2	1.0	0.2	1.2	4	..	..	3	
7	33	..	26	22	21	11.0	..	0.9	0.5	1.2	4	..	..	7	11
8	69	21	50	23	27	19.0	6.3	0.8	1.1	3.2	4	..	..	13	12
9	79	26	77	26	32	11.0	9.1	2.1	..	1.6	2	..	6	..	15
10	70	26	67	26	23	0.7	2.5	4.0	1.3	1.0	2	..	10	9	16
11	37	14	52	..	12	0.5	6.2	5.3	..	0.5	1	4	3		
12	35	17	32	19	..	0.6	18.0	6.0	0	0	7	14	4	0	0
13	19	..	30	9	10	14.0	22.0	6.0	0	0	5	12	12	0	0
14	24	..	..	..	..	25.0	4.3	0	0	0	27	14	10	0	0
15	..	15	19	..	4	0.6	0.5	1.7	0	0	43	..	11	0	0
16	..	..	8	4	..	10.0	..	1.1	0	0	43	..	6	0	0
17	9	9	2	..	..	3.5	0.6	..	..	..	37				
18	..	..	..	..	..	2.4	..	..	..	..	25				

Dog 39–194—first day of observation is 11 months after splenectomy; Dog 40–115—2 months after splenectomy.

Table 2 shows the results obtained with anemia by bleeding in 2 splenectomized dogs. The absolute number of normoblasts and basophilic erythroblasts here are much lower than in the acetylphenylhydrazine experiments, probably because the red cell level was considerably higher. Notwithstanding this the results obtained differ markedly from those obtained in normal dogs, in which it is well known that the normoblasts are very scarce during the recovery of this type of anemia.[6]

TABLE 2.—ANEMIA BY HEMORRHAGE.

Days of observation.	Hemoglobin (gm. per 100 cc.).				Normoblasts (thous. per c.mm.).				Ratio basophilic erythroblasts to normoblasts (%).	
	Splenectomized dogs.		Non-splenectomized dogs.		Splenectomized dogs.		Non-splenectomized dogs.		Splenectomized dogs.	
	39–194	40–115	35–4	39–1	39–194	40–115	35–4	39–1	39–194	40–115
1	5.2	6.3	6.2	5.5	0	0.7	0.6	..	0	
2	..	..	..	..	2.9	2.5	..	..	13	8
3	..	..	..	..	..	..	0	0		
4	..	..	..	..	6.2	13.0	1.0	0.2	30	25
5	..	..	..	..	5.0	10.0	1.3	0.4	16	10
6	..	..	..	..	3.0	15.0	..	..	20	6
7	..	..	..	..	1.5	1.7	0	0		
8	7.9	7.6	..	8.1	..	..	0	0		
9	..	..	9.0	..	0.9	0	0	0		
10	..	..	..	..	..	..	0.3	0.3		
11	..	..	..	..	..	..	0	0.6		
12	..	..	..	..	..	..	0.3	0.3		
13										
14	..	..	..	..	..	..	0	0.6		
15	..	..	..	9.4	..	..	0			
16	..	..	11.0	..	..	..	9			

Dogs 40–115 and 39–194 have been made anemic by 3 daily bleedings of 300 cc. each.

Dogs 35–4 and 39–1 are dogs of the anemic colony kept at low hemoglobin levels by bleeding. In these dogs no basophilic erythroblasts were found.

Dog 39–194—first day of observation is 11 months after splenectomy; Dog 40–115—2 months after splenectomy.

TABLE 3.—DOG 24–70, SPLENECTOMIZED ANIMAL.

Date.	Red blood cells (mil. per c.mm.).	Hemoglobin (gm. per 100 cc.).	Normoblasts (thous. per c.mm.).	Ratio basophilic erythroblasts to normoblasts (%).	Observations.
1927–12–19	1.3	3.9			
1928– 1– 3	3.4	6.7	57.0	33	
1– 9	3.6	9.3			
1–16	3.0	9.3	31.0	23	
1–23	4.1	10.8			
2–27	2.3	6.5	44.0	13	
3– 5	3.6	9.9			
4–21	..	7.2			
5– 1	3.4	9.0	77.0	8	7th day after hemorrhage (395 cc.)
5– 8	..	10.9			
5–31	..	6.2			
6– 4	1.8	..	20.0	15	6th day after hemorrhage (190 cc.)
6–11	..	8.7			
6–28	3.2	6.2			
7– 2	3.4	6.5	11.0	18	6th day after hemorrhage (165 cc.)
7– 9	4.5	8.5			
12– 3	..	5.8			
12–10	3.4	6.5	19.0	19	6th day after iron administration
12–17	..	9.7			

Splenectomy, June, 1925.

Table 3 indicates the most intense normoblastic crises observed. Blood smears and counts obtained once each week for a year's period of splenectomized Dog 24–70, were available for study. Examining this material we found 7 instances of marked normoblastic crises, all of which were related to regenerative periods as shown in the table. Perhaps these high normoblastic crises are

related to the fact that this dog was observed 2½ years following splenectomy, whereas the other 2 splenectomized dogs were studied for only 2 and 11 months respectively following the operation. In 4 instances we observed as Drinker and associates pointed out, the peak of normoblastic crisis occurred one week following the hemorrhage.

For comparison concerning the high human normoblastosis, we studied a case of anemia (thalassemia, Cooley's anemia) which showed the following results: C. J., female, aged 8: Red blood cells, 2,200,000 per c.mm.; hemoglobin, 4.6 gm. per 100 cc. blood; normoblasts, 70,000 per c.mm.

TABLE 4.—NORMOBLASTOSIS DURING LOW AND ACTIVE REGENERATION PERIODS.

During low regenerative period.			During active regenerative period.		
Dog No.	Average Hb. output per week (gm.).	Normoblasts (thous. per c.mm.).	Dog No.	Average Hb. output per week (gm.).	Normoblasts (thous. per c.mm.).
37-21	2	0	34-146	36	0.3
37-89	2	0	36-14	60	0
37-87	2	0	40-26	37	0.3
35-4	2	0.6	39-77	40	0
37-22	2	0	39-2	45	0
39-1	2	0	35-6	40	0
			32-4	37	0.9

Previous experience indicated that the normoblasts were not numerous during the regeneration period following anemia by hemorrhage in dogs, or in human anemias due to iron deficiency.[1] In order to obtain quantitative data of this subject, as well as for purposes of checking previous results, smears of 13 dogs were carefully studied. The results are given in Table 4 representing findings obtained in 6 dogs during a low regenerative period (2 gm. of hemoglobin as a weekly output) and 5 dogs during periods of active regeneration (between 36 and 60 gm. of hemoglobin weekly).

It may be of interest to point out that the normoblasts are of minor importance in the morphologic picture of the blood in human anemias in which there are no marked spleen changes. The iron-deficient anemias (anemia of childhood, anemia of pregnancy, nutritional hypochromic anemia, hookworm anemia, recovery from acute hemorrhage) serve as examples. In contrast, the largest normoblastic crises found in human pathology are associated, at least in the majority of cases, with blood diseases in which the spleen is involved and the blood shows signs of regeneration such as malaria with splenomegalia, hemolytic icterus, sickle-cell anemia, and particularly in the Mediterranean anemia (thalassemia).

Summary and Conclusions. Detailed morphologic blood cell examinations were made in 3 splenectomized and 19 non-splenectomized dogs.

In the splenectomized dogs made anemic by bleeding or by acetylphenylhydrazine injections, the number of normoblasts in the peripheral blood during the first phase of the regenerative period

is four times greater than in the non-splenectomized animal. In some instances the number may be even higher, attaining 70,000 normoblasts per c.mm. Furthermore the number of primitive erythroblasts (basophilic erythroblasts of Ferrata) is much higher in the splenectomized animal, in some cases reaching about 40% of the nucleated red cells in the circulation.

These findings suggest a relationship between a function of the spleen and the maturation of the erythroblast in the bone marrow or a factor acting upon the launching mechanism of new red cells into the general circulation.

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THE HEART IN SICKLE CELL ANEMIA.

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Since 1910 when Herrick[14] first described sickle cell anemia, many reports have appeared concerning the clinical, pathologic and hematologic aspects of this interesting disease. It has been said that these patients frequently suffer organic valvular disease of the heart.[1a,b] The purpose of this communication is to analyze the clinical and pathologic material of this hospital in order to determine the incidence and extent of organic heart disease among patients with sickle cell anemia.

Many of the symptoms that are present during exacerbations of this disease are similar to those of acute rheumatic fever; and many of the cardiac signs observed during the quiescent stage closely resemble those of chronic valvular heart disease, particularly mitral stenosis.

In his original paper, Herrick[14] described symptoms of exertional dyspnea, palpitation and recurring bouts of polyarthritis. His patient had an enlarged heart, with a loud systolic murmur over the whole precordium, and an accentuated second pulmonic sound.

In 1923, Huck[15] described in detail the hematologic changes of sickle cell anemia and gave a full clinical description of 2 cases. In addition to the findings first noted by Herrick, 1 of Huck's patients had a protodiastolic gallop and both had slight edema of the ankles, slight enlargement of the liver, a rapid, labile pulse and low blood pressure.

During the next few years, other papers[9,13,16,26] appeared, describing cases with cardiac enlargement, systolic murmurs, and accentuated second pulmonic sounds. Sydenstricker[26] was the first to report enlargement of the heart confirmed by Roentgen ray. He believed the polyarthritis, edema of the ankles and cardiac signs to be manifestations of the long-standing anemia. Hein, McCalla and Thorne,[13] however, regarded the dyspnea as due to the anemia but considered the possibility that the cardiac signs, fever, leukocytosis and joint symptoms represented atypical rheumatic infection. They noted, however, that the response to salicylates was not so prompt as in rheumatic fever.

In 1932, Anderson and Ware[1a,b] reviewed the literature and stated that cardiac enlargement was present in 76% and heart murmurs in 87% of the cases in which specific mention was made of their presence or absence. These authors came to the conclusion that the murmurs were probably functional but that organic heart disease was also present in many cases. Hamman[11] was the first to report an autopsied case of sickle cell anemia in which a definite diagnosis of rheumatic heart disease had been made. This was the first reported case in which diastolic murmurs were heard. Autopsy showed only a diffusely enlarged heart with normal valves and pericardium.

Although electrocardiograms had been taken on several patients,[11,29] no definite abnormality was observed until 1933, when King and Janeway[17] described a case with prolongation of the *P–R* interval. This finding in a young patient with cardiac abnormalities and recurring attacks of polyarthritis, fever, and leukocytosis made the possibility of rheumatic fever quite likely. This case (J. N.) is reviewed again in this report.

Postmortem findings were reported by many authors[8,9,11,13,15,25,26,29] and the only abnormality found in the heart has been hypertrophy and dilatation. Steinberg[25] observed that the hypertrophy usually involved the left ventricle more than the right. Marked right ventricular hypertrophy was found by Yater and Hansmann[29] in 2 patients who died in right-sided heart failure. In these 2 cases, there were either small thrombi in the pulmonary arteries or tortuous, thickened pulmonary vessels which the authors felt explained the right-sided failure.

There is only one reported instance in which any endocardial abnormality was found. In Steinberg's case[25] on which no clinical data are given, there was "chronic verrucose endocarditis of the mitral and aortic valves with mononuclear infiltration and patchy necrosis of the myocardium." He thought these changes to be of atypical rheumatic origin. No other myocardial and no pericardial lesions have been noted.

Case Material. Twelve patients, 8 males and 4 females, from 8 to 27 years, with average age of 19, were selected from the clinics

of this hospital for this study. All have severe sickle cell anemia with hematocrit values ranging from 20% to 30%, and the average duration of the anemia is 11 years. Most of the studies of cardiac function were carried out after the patients had been in bed for several days in the hospital.

Of the 11 fatal cases, all followed in this hospital, autopsies were performed on 10 at this hospital and on 1 at the Baltimore City Hospital. In this group of fatalities there were 6 males and 5 females from 2 to 28 years, with an average age of 11, and the average duration of the anemia was 8 years.

All the patients in both groups were negroes.

Clinical Data. No effort will be made to record all the findings in the clinical study of the 12 patients now alive. Only the data relative to the cardiovascular system will be reviewed and analyzed in an effort to compare the heart in sickle cell anemia with that in other anemias and in rheumatic valvular disease.

One case is reported here in some detail in order to illustrate the difficulties that may be encountered in differentiating sickle cell anemia from rheumatic fever and rheumatic heart disease.

Case Report. CASE 1.—J. N. (Unit No. 122176, Patient 7, Table 1) was a 21-year-old unmarried negress who had been followed in this hospital for 12 years. At the age of 9, she was first admitted to the Harriet Lane Home because of an upper respiratory tract infection of 3 weeks' duration, with generalized aching, headaches, epistaxes, exertional dyspnea, and pain in the right chest suggesting pleurisy. She had suffered occasionally from anorexia and post-prandial vomiting for several years.

Examination showed a fairly well-developed child with pallor and slight general glandular enlargement. Temp. 100°. The tonsils were large and pale. There were a few fine moist râles at the lung bases. Pulse was rapid, regular, quick and full. A capillary pulse was present. Blood pressure 100/50. The heart was enlarged to right and left, with a readily visible precordial impulse. The point of maximum impulse was outside the nipple line in the fourth interspace. No thrills were felt. The heart sounds were normal except for an accentuated P_2. A systolic murmur was present at the base and apex, and at the apex a low-pitched diastolic murmur was also present. The liver was enlarged but there was no abdominal tenderness, and there was no edema or orthopnea.

It was the impression of all who saw the patient that she had acute rheumatic fever and active rheumatic heart disease. There was a severe sickle cell anemia with leukocytosis. Roentgenogram showed cardiac enlargement and the electrocardiogram showed a heart rate of 107 with a P–R interval of 0.18 to 0.20 second. She was treated with salicylates which had no apparent effect. Low grade fever, leukocytosis, and the anemia persisted, and she had frequent epistaxes but no joint pains. She remained on the ward 5 months during which time the cardiac murmurs persisted and frequent electrocardiograms continued to show a prolonged P–R interval.

For the next 3 years, this patient was followed carefully in the Harriet Lane Clinic. At the age of 10, she had one attack of pain and swelling of the right ankle which lasted only 2 days. All the signs noted above persisted and a third heart sound appeared at the apex. The A–V conduction time was always prolonged, varying from 0.20 to 0.25 second and the cardiac enlargement increased slightly.

TABLE 1.—SUMMARY OF SOME IMPORTANT CARDIOVASCULAR FINDINGS IN SICKLE CELL ANEMIA.

Case No.	Age.	Sex.	Hematocrit, vol. %	Exertional dyspnea.	Murmurs.		Third heart sound.	Cardiothoracic ratio, %	Joint symptoms.	P–R interval, sec.	B.P., mm. Hg.	Ven. pressure, mm. saline.	Circulation time.	
					Systolic.	Diastolic.							NaCN, sec.	Paraldehyde, sec.
1. J.H.	8	M	20	No	+	0	+	53.0	No	.16	105/50	80	14.0	..
2. E.C.	9	M	23	Yes	+++	+	+	53.8	Yes	.15–.24	100/50	65	9.0	5.0
3. L.N.	14	F	20	No	+++	+	+	55.1	No	.16	120/65	95	10.2	6.0
4. G.E.	19	F	20	Yes	++	0	+	52.7	Yes	.16	116/60	70	17.0	No end point
5. J.N.	20	M	30	No	+	0	+	51.8	Yes	.16–.24	120/70	125	19.0	No end point
6. E.A.	20	M	20	Yes	+++	+	+	51.0	Yes	.16–.21	130/50	70	10.0*	6.0
7. J.N.	21	F	27	Yes	+++	+	+	58.0	Yes	.18–.24	110/55	65	20.0	10.0
8. E.E.	22	M	20	Yes	++	+	0	48.7	Yes	.16	110/60	55	12.3	6.5
9. S.L.	22	M	30	No	+++	+	+	53.0	Yes	.16	100/60	60	12.0*	5.0
10. J.M.	26	F	20	Yes	++	+	0	59.3	Yes	.18–.23	115/50	95	15.6	7.0
11. L.H.	26	M	20	Yes	+++	+	+	54.0	No	.21–.25	118/64	100	14.0	8.0
12. D.J.	27	M	23	No	+	+	+	51.2	Yes	.18	120/60	40	17.0	8.0

* C.T.T. (2 cc.) used instead of sodium cyanide.

She continued to have frequent epistaxes and exertional dyspnea increased. She had episodes of polyarthralgia but was not disabled until the age of 15 when she suffered an acute exacerbation with fever, headache, epistaxis, and pain in the left knee. She was admitted to the Medical Service for study, although the arthralgia and fever had already subsided.

Examination showed a well-developed, adolescent negress with pallor and jaundice. The temperature was normal. The pulse was increased in rate, quick, and full, and there was a capillary pulse. Blood pressure 100/45. The heart was enlarged, with accentuated P_2, loud systolic murmur at apex and base, and a third heart sound at the apex. Several observers heard a low-pitched rumble after the third sound. She had a marked anemia and leukocytosis. The *P–R* interval was slightly prolonged, 0.19 to 0.22 second. Roentgen ray showed cardiac enlargement without prominence of the pulmonary conus. Arm-to-tongue circulation time was 15 seconds with Decholin. Her course was marked by recurrent epistaxes and slow, slight improvement in the anemia.

At the age of 17, she was readmitted with severe pain in the left leg, ankle, and left side of abdomen. The onset was acute 3 days before admission and closely followed a mild upper respiratory infection. The patient voluntarily stated that the pain seemed to be in the bones rather than in the joints.

Examination showed no objective change in the joints but the left leg was extremely tender over the tibia. Cardiac findings were essentially as before. The anemia and leukocytosis persisted and the sedimentation rate was repeatedly normal, in spite of the severe anemia.* The *A–V* conduction time varied between 0.19 and 0.22 second. Roentgen rays showed no abnormality of the left tibia, but the cardiac enlargement persisted.

Salicylates were given a thorough trial and did not affect the pain; the left ankle actually became swollen during the course of treatment.

One year later, the patient had an acute attack of polyarthritis with some swelling of the shoulders, elbows, wrists, knees, and ankles. This

* This phenomenon has been shown by Bunting[5] to be due to the presence of sickled cells.

cleared up in a few days but was followed by severe nausea and vomiting which required admission to the hospital. Temp. 101°. Blood pressure 105/60. The joints showed nothing abnormal. The cardiovascular system revealed the same abnormalities as on previous admissions, and the liver was enlarged. The anemia, leukocytosis, normal sedimentation rate, and prolonged P–R interval were still present. During the 6 weeks that she was on the ward, the patient had repeated attacks of abdominal pain, with and without fever, and contracted Type III pneumococcus pneumonia, during which the sedimentation rate increased.

During the 3 years since this last medical admission, she has had only occasional epistaxes and mild arthralgias in damp weather. Exertional dyspnea has not increased. Her main complaint has been repeated attacks of abdominal pain, usually in the right lower quadrant with nausea and vomiting.

Five months ago, at the age of 21, a normal appendix was removed during one of these attacks. The postoperative course was uneventful. Examination 4 days after operation revealed a well-nourished, intelligent negress with pallor and icterus. The heart was enlarged to right and left, with an overactive precordium. The pulse was quick and full. Blood pressure 110/55. The point of maximum impulse was in the fourth interspace 8 cm. to the left of the midline and the heart shifted with change of position. The sounds were loud, with accentuation of P_2. A loud systolic murmur was present at apex and base. A loud third heart sound was present at the apex and a stethocardiogram showed a short presystolic sound which could not definitely be distinguished on auscultation. The liver was felt 4 to 5 cm. below the costal margin. There was no edema, orthopnea or dyspnea.

The severe anemia was still present. The P–R interval was 0.20 second and the teleroentgenogram is shown in Figure 4. Venous pressure, circulation times, and vital capacity were within normal limits. Fluoroscopy showed diffuse cardiac enlargement with no displacement of the barium-filled esophagus.

The patient was discharged a week later and has not returned.

In summary, this 21-year-old negress has had severe sickle cell anemia for at least 12 years. She has cardiac enlargement with signs suggesting rheumatic mitral disease and acute episodes with arthritis, fever, abdominal pain, and leukocytosis suggesting rheumatic fever. A–V conduction time has been prolonged on numerous occasions. In spite of the long duration of her illness, she has never had myocardial insufficiency of any noticeable degree, and the left auricle is not disproportionately enlarged.

Symptoms. Nine of the 12 patients complain of recurring attacks of pain in the joints of the extremities, frequently with swelling, and occasionally with increased heat and redness. The involvement of the joints is occasionally migratory. The pain, however, is often not localized to the joints but also involves the long bones of the extremity. Several patients have had an inflammatory reaction in the joint with swelling, redness, increased heat, and pain on motion. Aspiration of one such joint yielded no fluid.

The bone and joint pains usually occur during a "crisis," which is frequently preceded by a respiratory tract infection. There is associated fever, icterus, and leukocytosis. The pain does not respond to salicylates. It seems probable that the symptoms in the extremities are due to a subperiosteal reaction, and occasionally changes in the periosteum can be found on Roentgen ray examina-

tion. None of the patients have had subcutaneous nodules or skin lesions other than leg ulcers.

None has so far exhibited frank evidence of congestive heart failure. This seems to occur only during the terminal stages. Seven of the 12 patients have exertional dyspnea, with or without palpitation, and 5 of these 7 are subject to the recurrent leg ulcers that are commonly associated with this disease. Two other patients with no exertional dyspnea also have leg ulcers. The ulcers are usually unilateral and it is interesting to note that there is usually a history of unilateral dependent edema of that extremity preceding the appearance of the ulcer.

No patient has dyspnea at rest, nocturnal dyspnea, orthopnea, precordial pain, or chronic cough.

Physical Findings. *General.* These patients are somewhat underdeveloped and undernourished, and a few are markedly retarded in their physical and mental development. One patient has many congenital bone abnormalities, including spina bifida, marked scoliosis, and tower skull. This latter abnormality is also present in several other patients. There is always pallor and a peculiar greenish-yellow hue to the scleræ. General glandular enlargement is very common. The liver is moderately enlarged to percussion but is difficult to palpate, does not pulsate and is not tender. The spleen is not now enlarged in any of these patients, although splenic enlargement was definite in 2 when they first came under observation 7 and 12 years ago. There is occasionally slight dependent edema of the ankles.

Fundus Oculi. Seven of the 12 patients have moderate to marked dilatation and tortuosity of the retinal veins, as shown in Figure 1. This has previously been reported by Harden.[12] This finding could not be correlated with the other cardiovascular abnormalities, the leg ulcers, or the duration of the anemia.

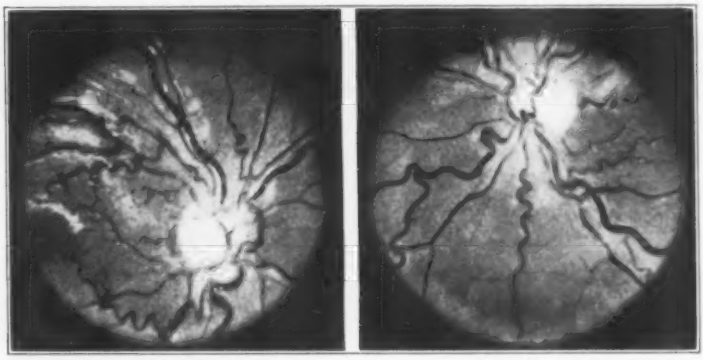
Cardiovascular. The pulse is normal in rate, quick but not collapsing, and of normal volume. There is frequently a sinus arrhythmia. Pulsations are prominent in the neck and often in the extremities. A capillary pulse is frequently visible, and pistol-shot sounds are often audible over the arteries. Duroziez's sign is rarely elicited. There is no venous distention, and the peripheral vessels are not sclerotic. The systolic blood pressure is normal, while the diastolic pressure tends to be low.

The precordium is overactive and this is often accentuated by the thin chest wall. There is a readily visible, diffuse, wavy impulse in the fourth, fifth and sometimes sixth interspaces to the left of the sternum. In cases with marked prominence of the pulmonary conus, there is a visible impulse and occasionally a bulge in the second and third interspaces to the left of the sternum. The point of maximum impulse is not well localized but is forceful and rolling, and there is a precordial lift. A diastolic tap is usually present in

the pulmonary area. A systolic thrill may be present over the precordium and vessels of the neck, but no diastolic thrill has been noted.

The heart is enlarged both to right and left and frequently there is increased dullness in the region of the pulmonary conus.

At the apex the first sound is louder than normal but not snapping. There is always a systolic murmur of variable intensity which is maximal early in systole and may be loud enough to obscure the first sound. The second sound is accentuated and in nearly every case there is a third heart sound early in diastole. No definite diastolic murmur is heard until presystole when there is often a questionable presystolic murmur blending with the first sound.



Right Eye. Left Eye.

FIG. 1.—Photograph of ocular fundi (D. J., Patient 12, Table 1) showing typical tortuosity and dilatation of the retinal veins.

At the base, there is a systolic murmur at the pulmonary area which may be louder than the systolic murmur at the apex. P_2 is markedly accentuated and occasionally split. No diastolic murmurs are definitely heard at the base. There may be a systolic aortic murmur transmitted to the vessels of the neck.

The heart shifts freely with change of position, and there are no signs of mediastino-pericarditis.

Roentgen Studies. The teleroentgenogram constantly shows cardiac enlargement. The heart is enlarged to both right and left and the enlargement increases as the patients develop. In 8 cases, the pulmonary conus is definitely more prominent than normal (Fig. 2). In 2 of these 8 cases, the pulmonary conus is extremely prominent (Fig. 3). In this patient (Fig. 3), a kymogram shows pulsations of branches of the pulmonary arteries. In 2 cases, the cardiac outline is globular (Fig. 4). The cardiothoracic ratio is increased in every case, with an average of 53.5%.

All the patients had a fluoroscopic examination with barium in

the esophagus and in no instance was there any displacement by a disproportionately enlarged auricle. The pulmonary conus appeared more prominent with the fluoroscope than in Roentgen ray films and the pulsations of the conus were more marked than the other heart borders. The cardiac enlargement seemed to involve all the chambers equally.

Electrocardiogram. At least one electrocardiogram was taken on every patient and frequent records were obtained on many. The striking abnormality was prolongation of the *P–R* interval in 50% of the patients (Table 1). This will be discussed more fully in another section.

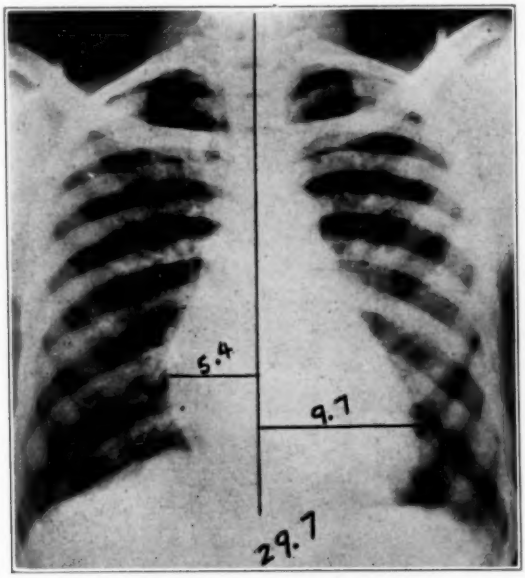


FIG. 2.—Teleroentgenogram (D. J., Patient 12, Table 1) showing cardiac enlargement with moderate prominence of pulmonary conus.

Sinus arrhythmia was frequently present and extrasystoles, usually of ventricular origin, were of common occurrence. Indeed, 1 patient had trigeminy and quadrigeminy which was thought clinically to be auricular fibrillation.

The *T* waves were sometimes altered, being unusually high in some tracings and lower than normal in others. The character of the *T* waves varied from time to time in the same patient. There was no significant axis deviation. Frank evidence of myocardial damage was lacking.

Stethocardiograms. Simultaneous electro- and stethocardiograms were taken on 9 of the 12 patients, principally to determine whether

there was a presystolic element in the sound at the apex. The portable Cambridge apparatus was employed, using Lead II for the electrocardiogram and the bell microphone to record the heart sounds. All the records were taken with the patients recumbent or semirecumbent.

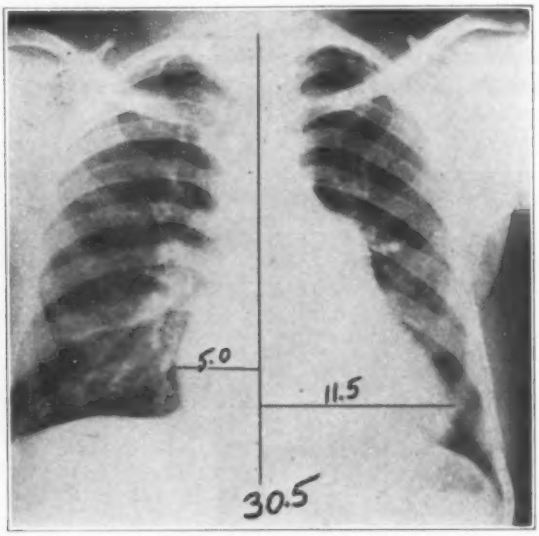


FIG. 3.—Teleroentgenogram (L. H., Patient 6, Table 1) showing cardiac enlargement with extreme prominence of pulmonary conus.

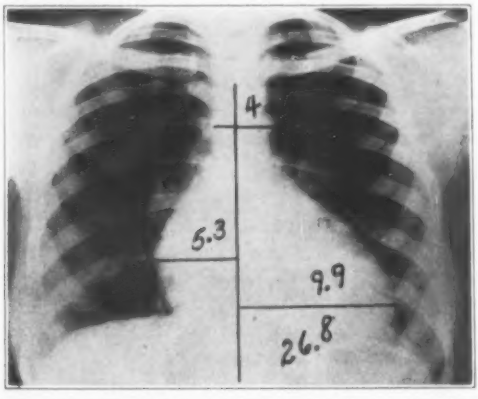


FIG. 4.—Teleroentgenogram (J. N., Patient 7, Table 1) showing diffuse cardiac enlargement with a globular configuration.

A typical record is shown in Figure 5. It is readily seen that there is a short, low-pitched presystolic sound which starts 0.10 sec-

ond before the first sound and 0.06 second before the *R* wave of the electrocardiogram. This occurred to a variable degree in all of the 9 patients and is indicated in Table 1 by a "+" under diastolic murmurs. This presystolic element was in general longer when the third heart sound was louder, but its intensity was not related to the length of the *P–R* interval.

The first sound is loud, but of normal pitch and is followed by a medium-pitched systolic murmur of moderate intensity which extends throughout most of systole. The second sound is slightly accentuated and followed by a short low-pitched sound of moderate intensity which is in the location of the normal third heart sound. Diastole is otherwise clear.

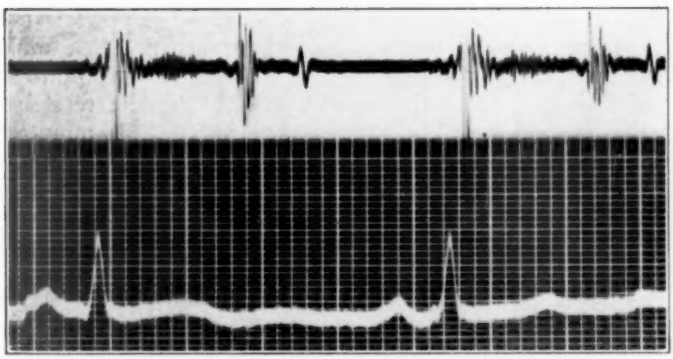


FIG. 5.—Stethocardiogram (D. J., Patient 12, Table 1) showing short presystolic murmur, systolic murmur, and third heart sound.

Tests of Cardiac Function. *Venous Pressure.* Determined by the direct method, this varied between 55 and 125 mm. saline (Table 1). Patient 6 (E. A.) was found to have a venous pressure of 200 mm. the first day of his fourth hospital admission 3 years ago. He had a mild streptococcal pharyngitis without fever, an enlarged liver, slightly distended cervical veins, and minimal edema of the ankles but no orthopnea or basal râles. The urine contained albumin (3+). On bed rest, the venous pressure fell to normal and the patient lost 2 pounds in 4 days. His venous pressure has not been found elevated since that time.

Circulation Times. In 10 patients, the arm-to-carotid sinus time was determined by the sodium cyanide method.[21] In the other 2, the arm-to-throat time was determined by the use of C.T.T. substance.[24] The arm-to-lung time was determined by the use of paraldehyde intravenously[6] (Table 1). In no instance were the circulation times definitely abnormal. It is interesting to note that they were not accelerated as is frequently the case in anemia.

Vital Capacity. No significant reduction from the estimated normal was found in those patients who were intelligent enough to coöperate.

P–R Interval. As noted above, a prolonged *A–V* conduction time was found in 6 of the 12 patients. The degree of prolongation varied considerably in each of the 6 patients, and in any given patient the *P–R* interval tended to increase as the heart rate decreased. The records of these 6 patients were carefully analyzed to determine whether there was any relation between the length of the *P–R* interval and the acute exacerbations of the disease; no correlation could be drawn.

To determine the rôle of anoxemia in causing this abnormality, 4 of these 6 patients were given varying concentrations of oxygen, by the method described by Levy.[18]

The patients were given 100% oxygen for 20 minutes and 10% oxygen for 10 minutes; no excess CO_2 accumulated. Electrocardiograms, using Lead II, were taken at intervals of 3 to 5 minutes. All these patients showed similar changes: upon exposure to 100% oxygen, the *P–R* interval increased and the rate decreased; with 10% oxygen, which could be tolerated for only 8 to 10 minutes, the *P–R* interval decreased and the rate increased.

Atropine sulphate (2 to 3 mg.) intravenously caused an increase in rate and decrease in the *P–R* interval.

One hundred per cent oxygen did not appreciably alter the atropine effect, and atropine did not potentiate the effect of 10% oxygen in decreasing the *P–R* interval. Ten per cent oxygen seemed to potentiate the effect of atropine in decreasing the *P–R* interval, probably through the increase in heart rate. A typical protocol is shown in Table 2.

Three patients with sickle cell anemia with normal *P–R* intervals showed no conduction changes with the two concentrations of oxygen or with atropine, although similar changes in rate occurred.

One patient with rheumatic fever with no anemia and with an *A–V* conduction time of 0.22 had no change in rate or conduction with the different concentrations of oxygen, but with atropine the rate increased and the *P–R* interval decreased to 0.17.

Three patients with pernicious anemia in relapse were tested in the same way. The first had angina pectoris and a *P–R* interval of 0.21. One hundred per cent oxygen did not affect the conduction time, although the rate decreased slightly. Ten per cent oxygen for 11 minutes produced precordial pain, a moderate increase in rate, and an increase in the *P–R* interval to 0.22. The second patient showed changes in rate with the different concentrations of oxygen and with atropine, but the *A–V* conduction time did not vary. The third patient, who was in a very severe relapse, showed the same changes that occurred in the sickle cell anemia patients but the initial *P–R* value was normal and the changes were of less degree. This patient was too ill to test with atropine.

TABLE 2.—EFFECT OF OXYGEN AND ATROPINE ON RATE AND CONDUCTION IN SICKLE CELL ANEMIA (PATIENT L. H.).

	Rate.	*P–R.*
First test. Control period	88	.22
10% oxygen started.		
After 3 min.	97	.20
6 "	103	.18
8 "	105	.18–.19
100% oxygen started.		
After 3 min.	67	.23
5 "	67	.25
10 "	68	.26
15 "	66	.25
20 "	68	.25
Second test. Control period	75	.23
3 mg. atropine SO_4—I.V.		
After 1 min.	93	.21
2 "	91	.21
4 "	91	.20
6 "	91	.20
8 "	91	.20
10 "	91	.20–.21
13 "	91	.20
Third test. Control period	79	.23
100% oxygen started and 3 mg. atropine SO_4—I.V.		
After 3 min.	83	.21
6 "	86	.20
10 "	86	.20
15 "	81	.21
17 "	81	.20
10% oxygen started.		
After 2 min.	83	.21
4 "	97	.19
7 "	103	.18

One patient with severe acute anemia from malaria inoculata was tested shortly after the malaria was terminated. He had a bradycardia of 50 and a *P–R* interval of 0.15. One hundred per cent oxygen produced no change in rate or conduction, while 10% oxygen slightly increased the rate and the *P–R* interval.

Table 3 summarizes the changes that took place in the arterial blood of the patient whose protocol is given in Table 2.

TABLE 3.—EFFECT OF 100% AND 10% OXYGEN IN SICKLE CELL ANEMIA (PATIENT L. H.).

	Control resting fasting.	After 100% oxygen for 20 min.	After 10% oxygen for 10 min.
P–R interval	0.23	.25–.26	.18–.19
Rate	79.0	67.0	111.0
Oxygen content arterial blood, millimols/liter	3.87	4.90	2.22
Per cent saturation arterial blood	89.3	112.8*	51.2
CO_2 content arterial blood, millimols/liter	24.6	24.3	23.6
Per cent sickled cells arterial blood	19.0	9.5	32.0
pH arterial blood	7.59	7.52	7.69
Serum sodium, m.eq./liter	136.0	136.2	135.2
Serum potassium, m.eq./liter	4.5	5.4	
Hemoglobin (Newcomer), gm./100 cc.	7.6	8.0	7.8
R.B.C., millions	2.72	2.84	2.72
Hematocrit, vol. % of packed R.B.C.	21.3	23.2	21.5

* Oxygen capacity of blood determined by saturating with *room air*.

Effect of 100% Oxygen. A marked increase occurred in the oxygen content of the arterial blood, while the CO_2 content and hydrogen-ion concentration did not change significantly. There was a marked decrease in the number of circulating sickle cells as determined by Sherman.[23] There was no alteration in the serum sodium or potassium and the values for hemoglobin, red blood cells, and hematocrit did not change significantly.

Effect of 10% Oxygen. As might be anticipated, there was a very marked decrease in the oxygen content and in the per cent saturation of the arterial blood. The CO_2 content and the hydrogen-ion concentration decreased slightly. The number of sickle cells increased markedly. The serum sodium and values for hemoglobin, red blood cells and hematocrit were not appreciably altered.

These results illustrate the marked anoxemia that these patients constantly suffer. They show that the anoxemia and *in vivo* sickling are increased when the *P–R* interval is shortened and the cardiac rate increased. When the anoxemia and *in vivo* sickling are decreased, the *P–R* interval is increased and the cardiac rate decreased. These findings are difficult to correlate in so far as cause and effect are concerned.

It is possible that the vagal tone is increased as part of the compensatory mechanism for the long-standing anemia. In support of this point of view is the fact that atropine, which temporarily blocks the vagus, has the same effect on rate and conduction as does a sudden increase in anoxemia.

Carotid sinus pressure had no effect in the above patient; it was not tried in other cases.

Pathologic-Anatomic Data. Eleven patients who had sickle cell anemia were examined postmortem. Only 4 were adults; the diagnosis of rheumatic heart disease had been made in 2 of these and questioned in 1 other. Her case history is presented in some detail.

Case 2.—H. B. (Unit No. 135000, Patient 11, Table 4). This 28-year-old negress was first seen in this hospital in 1930 at the age of 18, complaining of weakness. She had always suffered poor health and for many years had had frequent attacks of polyarthritis. These usually occurred in the winter in association with sore throats and were accompanied by jaundice. At 15, she had apparently had acute glomerulonephritis. Examination showed a poorly nourished, underdeveloped girl with marked pallor and jaundice. The temperature was 101°. Blood pressure 125/80. The heart was enlarged to right and left, and Roentgen ray showed a prominent pulmonary conus. The sounds were rapid, regular and loud with marked accentuation of P_2. There was a loud systolic murmur over the whole precordium and at the apex, a third heart sound and an indefinite presystolic rumble. The liver was enlarged. The lungs were clear and there was no edema. Laboratory examinations showed a severe sickle cell anemia which persisted throughout the next 10 years, and evidence of chronic nephritis. Electrocardiogram was normal.

A few months later, she was admitted again because of epigastric pain, nausea, and vomiting. While under observation, she had a "crisis" with generalized bone pain which was followed by transient swelling over both ulnæ.

She then felt quite well until the age of 24 when she first noticed exertional dyspnea and ankle edema. One year later, she became pregnant and her symptoms became so severe that an abdominal hysterotomy was done. At this time, the late diastolic rumble was more definite. Kidney function was markedly impaired with some azotemia.

TABLE 4.—PATHOLOGIC DATA IN SICKLE CELL ANEMIA.

Case No.	Age.	Sex.	Average normal heart weight (gm.).	Actual heart weight (gm.).	Per cent increase.	Remarks.
1. A. P.	2	M	60	90	50	Cardiac failure during crisis 1 year before death; died of pneumococcal meningitis.
2. A. C.	2	F	56	70	25	Died in crisis.
3. M. B.	2	F	56	110	96	Died of bronchopneumonia.
4. J. S.	3	M	65	125	92	Died in crisis.
5. T. H.	3	M	65	95	46	Died in crisis.
6. C. S.	5	M	85	150	76	Died in crisis.
7. D. S.	6	F	94	140	48	Died of cirrhosis of liver.
8. P. S.	15	F	200	280	40	Clinical diagnosis of rheumatic heart disease; died in crisis.
9. J. J.	22	M	300	440	47	Died in uremia, heart failure; cirrhosis of liver.
10. W. B.	24	M	310	480	55	Clinical diagnosis of rheumatic heart disease; died in uremia, heart failure.
11. H. B.	28	F	270	460	70	Died in uremia, heart failure.

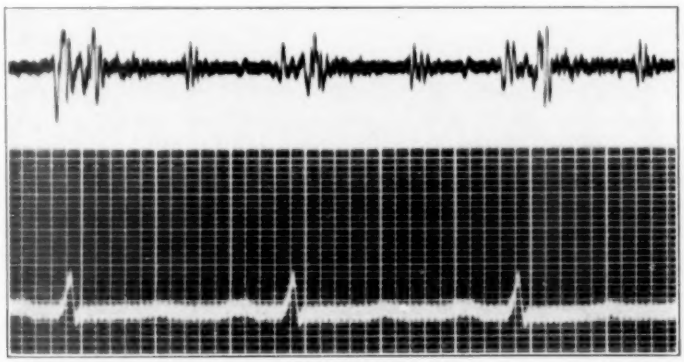


FIG. 6.—Stethocardiogram (H. B., Table 4) showing loud presystolic element, systolic murmur, and third heart sound.

She worked as a housekeeper for the next year and felt remarkably well. The dyspnea, edema, weakness and epigastric pain returned, however, and one year before death, she was again admitted to the hospital with definite evidence of cardiac failure. Blood pressure 170/85. The cardiac signs remained as before but there was edema, pulmonary congestion, elevation

of venous pressure, and hepatomegaly. The signs of heart failure improved very slowly on bed rest and digitalis, and blood pressure fell to normal, but the non-protein nitrogen slowly rose and renal function grew progressively worse.

She continued to take digitalis after discharge but heart failure returned, and 4 months before death she was once more admitted. Blood pressure 150/80. The heart had further increased in size, and the signs were much as before. Figure 6 shows the loud presystolic sound that was present. This was interpreted by some as a murmur, by others as a gallop.

She was admitted for the last time in January, 1940, suffering with severe congestive heart failure, uremia, and slight hypertension, 160/75. She died after 3 days with terminal pneumonia.

Anatomic Diagnosis (Dr. R. Follis). Sickle cell anemia with extreme fibrosis and shrinkage of spleen. Chronic glomerulonephritis. Hemosiderin in kidneys. Cardiac hypertrophy and dilatation. Myocardial scars, slight. Hydropericardium. Lobular pneumonia. Chronic cholecystitis, with cholelithiasis.

The heart was enlarged in every case (Table 4). The estimated normal weights are obtained from the tables of Coppoletta and Wolbach[7] and Roessle and Roulet.[22] The cardiac hypertrophy was diffuse in all cases.

The endocardial surfaces and valves were normal in every case. There was moderate dilatation of the pulmonic orifice in several instances. In Patient 11, where the pulmonic conus was prominent on Roentgen ray, the ring was definitely dilated. The pericardial surfaces were always normal. Except for some hypertrophy of the muscle fibers, the myocardium showed no constant changes. No Aschoff bodies were found.

The lungs showed edema in more than half the cases and bronchopneumonia in several. No case showed any such striking changes in the pulmonary vascular tree as described by Yater and Hansmann.[29]

The liver was uniformly enlarged, except in the 2 patients who had cirrhosis. There was usually mild chronic passive congestion with deposition of pigment and occasionally central necrosis.

The kidneys uniformly contained large deposits of hemosiderin in the convoluted tubules. There was a far-advanced nephritis in 2 patients, glomerulonephritis in Case 11 and a peculiar nephritis of undetermined type in Case 9. In Patients 5 and 8, there was slight scarring of the cortex.

Discussion. Cardiac hypertrophy due to anemia has been produced experimentally in dogs by Lüdke and Schüller.[19] Cardiac enlargement in pernicious anemia has frequently been noted clinically and at autopsy; and these patients may also have physical signs strongly suggesting valvular disease.

In 1931, Ball[2] reported the first case in which Roentgen ray evidence of cardiac enlargement in a young woman with hypochromic microcytic anemia disappeared after 3 months as the anemia re-

sponded to treatment. The patient also had the physical signs of mitral stenosis and these likewise disappeared.

Gunewardene[19] has reported several cases of chronic hookworm anemia with cardiac enlargement, systolic and diastolic murmurs at apex and base, and mild congestive failure. As the anemia improved, the unusual cardiac signs disappeared. Only 1 patient died; the heart in this case was found to be hypertrophied and dilated, with normal valves and endocardium.

In 1937, Porter[20] carefully studied cardiac function in severe hookworm anemia and found cardiac enlargement, confirmed by Roentgen ray examination, with systolic murmurs. The heart rate and blood pressure were normal in the adults, and congestive heart failure was not a prominent feature. Venous pressure and circulation time were normal and the vital capacity was not reduced. Electrocardiograms were normal except in one 23-year-old woman who had a P–R interval of 0.21. Unfortunately a record was not obtained after improvement had taken place. In the majority of cases, the heart decreased in size as the anemia improved. The other cases showed no decrease by Roentgen ray examination, but they were followed for only 6 to 8 weeks and it seems probable that all the hearts would have decreased in size had the patients been followed for a longer period.

Thus it is apparent that any severe anemia of sufficient duration may be responsible for the cardiac signs that are present in sickle cell anemia. The signs are probably more pronounced and more frequent in sickle cell anemia because of its chronicity and resistance to treatment.

Records of 2 cases of chronic hemolytic jaundice, which may closely resemble sickle cell anemia, were found in the files of our Pathological Department. Both had enlarged hearts, with systolic and diastolic murmurs, and at autopsy showed cardiac hypertrophy with normal valves and endocardium.

A late diastolic murmur at the apex has been noted in other conditions in which the mitral valve was later found to be normal. Wood and White[27] mention its presence in 4 patients with diffusely enlarged hearts, while Wyckoff and Bunim[28] note its occurrence in cor pulmonale. Bland, White and Jones[4] discuss the significance of a presystolic apical murmur in 32 patients with acute rheumatic carditis. None of these had cardiac murmurs when examined 8 years later. These authors suggest that myocardial weakness and ventricular dilatation create a "relative mitral stenosis" when the mitral ring does not stretch as much as the ventricle dilates. The same conditions could account as well for the presystolic murmur that is present in sickle cell anemia.

In 1937, Bartels[3] reported a case of severe congestive heart failure in a 76-year-old white male who had a severe chronic posthemor-

rhagic anemia from a bleeding peptic ulcer. The patient made a rapid recovery when treated at rest with salyrgan and iron. No digitalis was ever administered, and several years later there was no evidence of myocardial insufficiency.

Congestive heart failure has not so far occurred in any of the living patients, although they probably have a diminished cardiac reserve which is not detectable by the methods used to study cardiac function. In the terminal stages, however, congestive heart failure commonly occurs.

The crises of sickle cell anemia closely mimic episodes of acute rheumatic fever with joint pains, fever, leukocytosis, cardiac enlargement and murmurs, and a prolonged *P–R* interval. The presence of anemia and jaundice in a negro with these findings should suggest to the physician that he examine the blood carefully. There are, however, two important points in which these crises differ from rheumatic fever: *first*, the history or presence of pain over the long bones as well as in the joints, and *second*, the failure to respond to salicylates.

Treatment. There is no specific or effective treatment for the anemia. Transfusions need not be given unless the patient is having a hemolytic crisis. These patients frequently have severe transfusion reactions and the benefit derived from transfusion is of short duration.

Digitalis has been of no aid in treating the congestive failure that occurs in the late stages of the disease, or during a hemolytic crisis. One child who had congestive failure during a severe hemolytic crisis one year before death, received digitalis to the point of intoxication without any improvement. His recovery from myocardial failure occurred promptly when the crisis had ended.

The recurrent leg ulcers are extremely difficult to heal. Adequate rest with elevation of the legs prevents the edema which usually precedes the ulcers. Variable results have been obtained by local excision, followed by grafting, and mecholyl iontophoresis. Lumbar sympathectomy has produced good results in 1 case.

Summary. 1. The heart is diffusely enlarged in patients with sickle cell anemia. There are usually systolic and diastolic murmurs and a third heart sound at the apex, and an accentuated second pulmonic sound with a systolic murmur at the base.

2. The *P–R* interval of the electrocardiogram is often prolonged.

3. The similarities between rheumatic fever and sickle cell anemia are discussed. In sickle cell anemia, pain is not confined to the joints and the response to salicylates is not striking.

4. Although the diagnosis of rheumatic heart disease has often been made in patients with sickle cell anemia, it has not yet been confirmed at autopsy.

5. Congestive heart failure, not responding to digitalis, is common only in the terminal stages of the disease.

6. The cardiac changes in sickle cell anemia are probably secondary to the severe long-standing anemia.

Conclusions. 1. No cause other than the profound anemia is found to explain the cardiac changes in patients with sickle cell anemia. The mechanism by which any anemia produces changes in the heart is not entirely understood, but it seems probable that the hypertrophy and dilatation are compensatory for the prolonged anoxemia.

2. The cardiac changes of patients with sickle cell anemia are more marked than the changes found in other anemias. This is because sickle cell anemia is somewhat unique in the long duration of such a severe degree of anemia.

3. The prolonged *A–V* conduction time is probably due to increased vagal tone, which also appears to be secondary to, or compensatory for, the prolonged anoxemia.

4. Although the clinical picture may closely resemble rheumatic fever, there is no proved instance of the two diseases occurring together. From the available data, there is no need to regard these patients as uncommonly liable to rheumatic fever.

I wish to thank Dr. G. W. Thorn for the blood chemical studies, Dr. M. M. Wintrobe and Dr. I. F. Sherman for the hematologic studies, and Miss Julia Ann Vickers and Miss Barbara Spraker for technical assistance in the Cardiographic Laboratory.

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A NOTE ON CARDIAC MURMURS.

Recommendation for a Revised Terminology.

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Several years ago it became apparent to us that the present classification of heart murmurs as *functional* and *organic* was not only unsatisfactory but confusing. The term *functional* is applied loosely to two distinct groups of murmurs: those found in the normal person and unaccounted for by the presence of cardiovascular or other disease, and those produced by pathologic dilatation of a valve ring, great vessel, or heart chamber. The same term, therefore, has for years been used to describe, on the one hand, a murmur of no clinical importance, and on the other, a murmur which may have serious implications.

The term *organic* is similarly unsatisfactory; as used today, it refers only to the murmurs caused by actual deformity of a valve. Yet serious organic disease of the heart muscle resulting in cardiac dilatation may in the absence of valve deformity cause a murmur. In infarction of the heart, for example, a systolic murmur due to mitral regurgitation is common, yet no valve deformity exists. To call this murmur functional conveys the erroneous impression that it has no serious import.

The terms "inorganic" and "accidental" are likewise unsatisfactory because of their inexact and vague connotation.

The true nature of the various types of murmurs is in our estimation more clearly indicated by the following nomenclature:

Physiologic Murmurs. A. Intracardiac or intravascular. B. Extracardiac. (*a*) Cardiopulmonary. (*b*) Pericardial.

Pathologic Murmurs. A. Due to structural valvular disease. B. Due to congenital cardiovascular defects. C. Due to dilatation of ventricles or aorta or pulmonary artery from: (*a*) Cardiovascular disease. (*b*) Other diseases, such as anemia, thyrotoxicosis, or severe infection. D. Due to pericarditis.

I. Physiologic Murmurs. These are frequently found in normal persons and may be intra- or extracardiac in origin.

A. *Intracardiac or Intravascular.* Almost all of these murmurs are systolic in time. They are most often heard over the pulmonic valve area, and the majority of the remainder are at the apex. They are usually short, rarely occupying all of systole, are soft and blow-

ing in quality, and are heard over a limited area. They are not associated with cardiac enlargement or any other evidence of heart disease. They may be louder at the end of inspiration but much more often at the end of expiration. They are likely to be evanescent or inconstant. They may appear after hard exertion and disappear within a few minutes or hours. They vary with the position of the body, being loudest as a rule in recumbency and often are heard only in that position.

B. *Extracardiac.* (*a*) Cardiopulmonary murmurs (short for murmurs within the lungs produced by the action of the heart). The term currently used to describe these murmurs, *cardiorespiratory*, should be abandoned because of its ambiguity; it is applied not only to murmurs arising in the lung—the true cardiopulmonary murmurs—but is also incorrectly applied to intracardiac or intravascular murmurs which happen to be heard more clearly in one phase of respiration (usually expiration) than in the other. Cardiopulmonary murmurs are usually systolic in time, rarely diastolic, they are blowing in quality, and relatively faint. They are thought to be the result of cardiac action on the lungs themselves in squeezing air from a small portion of the lung overlying the heart by compression and of drawing air into the lung adjacent to the heart by suction. Since both vary with respiration, it is sometimes difficult to differentiate true cardiopulmonary murmurs from physiologic murmurs of intracardiac or intravascular origin. (*b*) Pericardial sounds. Superficial scratchy sounds of short duration, systolic or diastolic or both, are occasionally heard along the left border of the sternum, particularly after exertion or under other circumstances of increased blood flow, as in thyrotoxicosis. They can probably be explained as due to compression of the pericardial surfaces by the vigorously acting heart or pulmonary artery. Ortiz has demonstrated that pericardial friction sounds can be produced by pressure on a normal pericardial surface.*

II. Pathologic Murmurs. These are systolic or diastolic and can be divided into three categories:

A. Those due to structural disease of the valves.

B. Those due to congenital cardiovascular defects.

C. Those found with dilatation of a vessel or chamber secondary to: (*a*) Cardiovascular disease, such as the apical systolic murmur of relative mitral insufficiency in a case of hypertension with pronounced left ventricular enlargement, or of rheumatic myocarditis, or of myocardial infarction. (*b*) Other disorders which secondarily affect the circulatory system, such as anemia.

D. Those due to acute pericarditis. These are systolic or systolic and diastolic in time, often scratchy, and usually best heard at the left lower border of the sternum or midway between that region and the apex. They may be designated simply as friction sounds.

* Ortiz y Ramirez, T.: Arch. latino am. de cardiol. y hemat., **3**, 45, 1933.

It is often difficult, indeed impossible, to decide whether a systolic murmur, when it is slight in degree, is physiologic or pathologic. Likewise, it is sometimes impossible to determine in the case of pathologic murmurs whether or not they are due to deformed valves. Moreover, both valvular deformity and dilatation of heart chambers or great vessels may be factors in the same case. Nevertheless this simple classification is one we have found to be far superior to the old one, and we recommend its adoption.

As examples of the use of this revised nomenclature of heart murmurs, we present an analysis of two groups of cases: (1) 100 Harvard freshmen (among the first 526 examined in 1939–40) who showed murmurs;* (2) 100 private patients.†

	Physiologic.		Pathologic.‡ Due to dilatation.		Pathologic.‡ Due to valvular deformity.	
Systolic.	Students.*	Patients.†	Students.*	Patients.†	Students.*	Patients.†
Pulmonic or basal	44	12	0	1	0	0
Apical	33	6	0	17‡	1§	22‡
Aortic	3	3	0	9	0	4
Left border alone	8	0	0	0	0	1
Apex and base	7	1	0	10‡	0	2‡
Precordial	4	2	0	1	0	0
Diastolic alone.						
Apex	0	0	0	0	0	2
Base	0	0	0	1	0	2
Apex and base	0	0	0	0	0	4
Total	99	24	0	39	1	37

¶ 29

* Courtesy of Dr. Arlie V. Bock, Professor of Hygiene, Harvard University.

† Records of Dr. Paul D. White.

‡ Undoubtedly in several cases both dilatation and valvular deformity were responsible factors.

§ This case showed also diastolic murmurs, mitral and aortic.

¶ Of these 29 cases, 27 showed also diastolic murmurs, mitral, aortic, or both.

THE EARLY DIAGNOSIS OF SYPHILITIC AORTITIS.*

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Syphilis is an important cause of heart disease that usually appears 15 to 20 years after the primary lesion. During the long

* This study was aided through a grant from the Isaac Kaufman Foundation, Montefiore Hospital.

latent period few cases with early syphilitic aortitis are recognized. In the majority of instances the diagnosis is made late in the disease when serious complications of aortitis are present, namely, aortic regurgitation, saccular aneurysm or stenosis of the coronary ostia.

The diagnosis at this late stage of the disease is of little value. Because the results of antisyphilitic treatment are dependent upon the stage of the disease in which it is started,[14a,28] it is very important that aortitis is recognized before complications develop. Early diagnosis, however, is very difficult. Many writers[3,7,31] recognize this although contrary views[10,15,17,18] are to be found. The purpose of this paper is to determine the feasibility of the diagnosis of early or uncomplicated syphilitic aortitis.

Material and Methods. The material used consisted of 200 syphilitic patients without saccular aneurysm, arterial hypertension or valvular disease and 200 individuals of the same age and sex without syphilis, this latter group being used as a control. The diagnosis of syphilis was based on the presence of repeated positive Wassermann and Kahn reactions of the blood. In the control group, syphilis was excluded by history, physical examination, which included neurologic examination, and repeated serologic investigation of the blood.

The study was limited to patients between 20 and 50 years of age free from roentgenographic and physical evidence of arteriosclerosis. Patients with abnormal elevation of the diaphragm or kyphoscoliosis were excluded from the study. Patients with past or present arterial hypertension and rheumatic aortic insufficiency were also excluded since dynamic dilatation has been reported in each of these conditions.[22]

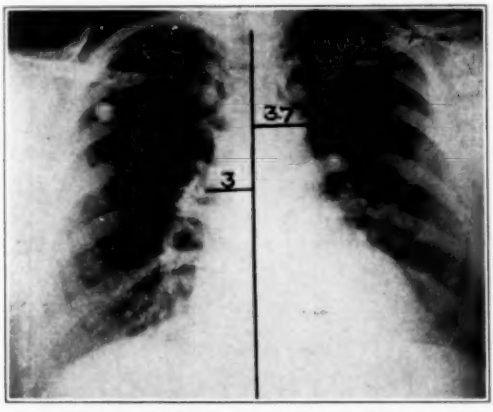

FIG. 1.—Vaquez-Bordet measurement of the aortic arch.

The following procedures were obtained in each patient: 1, a teleroentgenogram and fluoroscopy; 2, a physical examination; and 3, an electrocardiogram. The roentgenograms were obtained in the postero-anterior and left anterior oblique positions, the latter at an angle of about 45 degrees. These were taken at the end of moderate inspiration, at a distance of 6 feet, with the patient standing. Physical examination was conducted in the

sitting position. The standard as well as the chest leads were used in obtaining the electrocardiograms. In the chest lead the right arm electrode was placed over the apex of the heart and the indifferent electrode on the left leg.

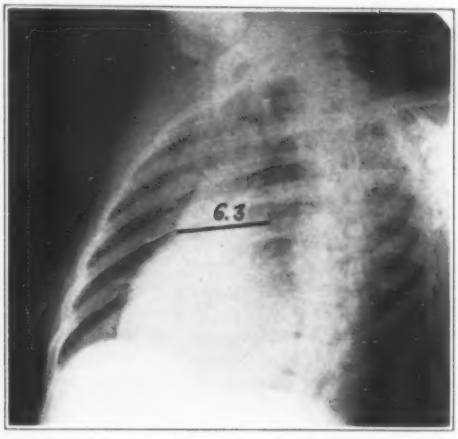

FIG. 2.—Hampton's measurement of the root of the aorta in the left oblique position.

The aortic arch and root were measured by three different methods: 1, Vaquez-Bordet[30]; 2, Hampton[10]; and 3, Fray.[9] These methods were studied since they have been suggested as means of recognizing syphilitic

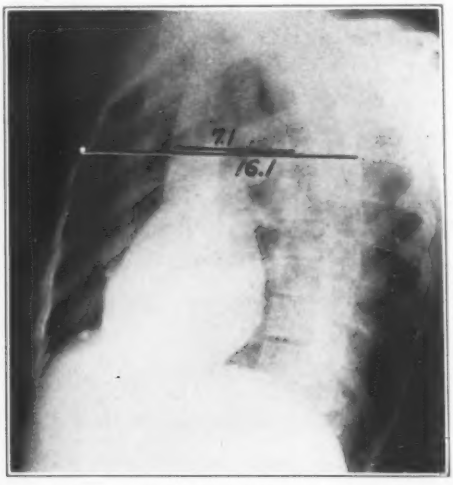

FIG. 3.—Fray's measurement of the aortic arch in the left oblique position.

aortitis. The width of the aortic shadow in the postero-anterior teleroentgenogram was obtained "by adding the measurement of the farthest point of the ascending aorta to the right of the mid-sternal line to the measure-

ment of the farthest point of the aortic knob to the left of the mid-sternal line"[30] (Fig. 1). The width of the root of the aorta in the left oblique position was obtained by drawing a transverse line from the "junction of the ascending aorta with the anterior border of the heart to the region of the pulmonary artery where it intersects the posterior border of the heart"[10] (Fig. 2). The aortic arch was also measured in the left oblique position in the manner indicated by Fray.[9] "A line was drawn transversely from the ascending limb of the arch to a corresponding point on the descending limb at this level. The chest measurement was taken at the level of the arch measuring from the right anterior chest wall to the left costovertebral articulation. The diameter of the chest was divided by the diameter of the arch to obtain a ratio called the transverse-arch-chest index" (Fig. 3).

Results. I. *Roentgen Examination.* (*A*) An analysis of the Vaquez-Bordet measurement in 200 normal patients revealed a wide variation in the size of the normal aorta. The latter measured 3.9 to 7.8 cm. No definite relation could be demonstrated between the size of the aorta and the race, sex, height, weight, chest diameter, occupation and age of the individual patient, although there was a tendency to an increase in the size of the aorta in obese or older patients. It is impossible to determine a standard of normal measurement on account of the marked variability of the normal aorta.

A summary and comparison of the Vaquez-Bordet measurement of 200 non-syphilitic and 200 syphilitic patients by age groups is shown in Table 1. The impressive feature of this comparison is that, with a few exceptions, the two groups present identical measurements. The increase in the size of the aorta is virtually the same with advancing years in syphilitic and non-syphilitic patients and is apparently due to arteriosclerosis.

TABLE 1.—A COMPARISON OF THE VAQUEZ-BORDET MEASUREMENT IN NORMAL AND SYPHILITIC SUBJECTS.

Age.	Extreme variations of aortic width (cm.).	Average aortic width (cm.).
20–30	3.9—6.6	5.0
20–30	*3.2—6.7*	*5.0*
31–40	4.8—7.6	5.8
31–40	*4.6—7.5*	*5.8*
41–50	4.7—7.4	6.2
41–50	*4.8—10.0*	*6.7*

Black—normal. Italic—syphilitic.

An analysis of the syphilitic group revealed the fact that 3% had unequivocal or diffuse aneurysmal dilatation of the thoracic aorta. The aortic shadow then has a characteristic fusiform or spindle-shaped appearance in the postero-anterior and oblique positions (Fig. 4). It is important to note that the roentgenologic diagnosis of syphilitic aortitis in these instances was made late in the disease, 18 to 20 years after the onset of the infection. Thus, it appears that the postero-anterior teleroentgenogram is of practically no aid in the early diagnosis of syphilitic aortitis but of distinct value in the late stages when wide dilatation of the aorta exists, since in

many instances it is the first or even the only sign to lead one to the proper diagnosis. Before making the diagnosis of diffuse aortic dilatation, however, the postero-anterior view must be supplemented by an oblique view for accurate diagnosis.[24] Otherwise, elongation and tortuosity of the aorta of sclerotic origin may be interpreted incorrectly as dilatation.

We attempted to determine the influence of arterial hypertension or advanced arteriosclerosis upon the width of the aortic arch. For this reason we studied a number of non-syphilitic patients between 40 and 50 years with hypertension as well as another group of patients between 50 and 70 years, with and without hypertension. We found, like other workers,[23] that wide aortic dilatation may exist with arterial hypertension or advanced arteriosclerosis. The result

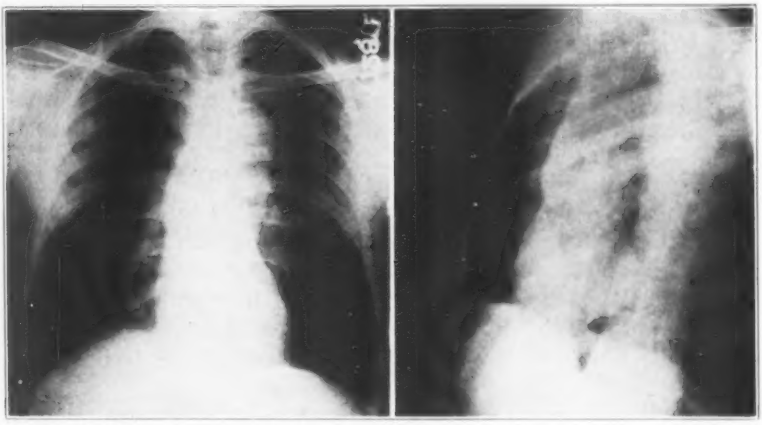

FIG. 4.—Posterio-anterior and left oblique teleroentgenogram illustrating diffuse dilation of the aorta.

is that in the complicating presence of these conditions it is impossible to recognize syphilitic aortitis by Roentgen ray before the advent of saccular aneurysm.

B. Hampton's[10] method of measuring the root of the aorta seems to be of little value in the early diagnosis of syphilitic aortitis. The root of the normal aorta measured 4 to 7.4 cm. This wide variation is responsible for the difficulty in obtaining a reliable standard of normal measurement.

Hampton's measurement fails to distinguish the syphilitic from the non-syphilitic aorta prior to the onset of marked aortic dilatation. A summary and comparison of the root measurement of Hampton in syphilitic and non-syphilitic individuals by age groups is presented in Table 2. With a few exceptions, the two groups present similar measurements. In our study the maximum root

measurement in a normal patient was 7.4 cm. rather than 6 cm. as reported by Hampton. Among 200 syphilitic patients without complications, only 2 cases (1%) presented root measurements above 7.4 cm. These cases had wide dilatation, recognized first by Roentgen ray 20 years after the primary infection.

TABLE 2.—A COMPARISON OF THE ROOT MEASUREMENT OF HAMPTON IN SYPHILITIC AND NON-SYPHILITIC SUBJECTS.

Age.	Extreme variations of aortic root (cm.).	Average aortic root (cm.).
20–30	4.0—6.2	5.18
20–30	*3.5—6.5*	*5.1*
31–40	4.0—7.0	5.5
31–40	*4.0—7.0*	*5.4*
41–50	4.0—7.4	5.6
41–50	*3.0—10.0*	*6.4*

Black—normal. Italic—syphilitic.

Seven and a half per cent of normal and 14% of syphilitic individuals presented root measurements between 6.2 and 7.4 cm. The increased incidence among syphilitics is no doubt significant since syphilis commonly involves the root or proximal portion of the aorta. But it is impossible to evaluate this fact clinically since Hampton's measurement fails to differentiate the syphilitic from the non-syphilitic aorta.

C. Fray[9] concluded from his studies of the aortic arch that the transverse-arch-chest index sharply differentiates the normal from the abnormal aorta. He found that the normal arch had a transverse-arch-chest index above 1.9 and that the pathologic or dilated aorta had a transverse-arch-chest index below 1.9.

Our findings indicate that Fray's index is of little value in the early diagnosis of syphilitic aortitis. We found: 1, that normal patients may have an index below 1.9; and 2, that the indices of normal patients were indistinguishable from those of syphilitic patients prior to the development of marked aortic dilatation. A summary and comparison of the indices by age group may be seen in Table 3. The lowest index in our normal group was 1.65 and occurred in a male of 35. Only 1 out of 200 syphilitic patients had an index below 1.65.

TABLE 3.—A COMPARISON OF THE TRANSVERSE-ARCH-INDEX OF FRAY IN NORMAL AND SYPHILITIC SUBJECTS.

Age.	Extreme variations of transverse-arch-index (cm.).	Average transverse-arch-index (cm.).
20–29	1.65—2.93	2.36
20–29	*1.75—2.75*	*2.33*
30–39	1.80—3.15	2.14
30–39	*1.65—3.15*	*2.31*
40–49	1.71—2.59	2.15
40–49	*1.55—2.32*	*2.03*

Black—normal. Italic—syphilitic.

Of the normal group 2.7% and of the syphilitic group 7% had an index below 1.9. The increased incidence may mean syphilitic aortic disease but it is difficult to evaluate this clinically.

D. Fluoroscopy has been suggested as an aid in the diagnosis of aortic syphilis. Local dilatation with increased pulsation or increased density and irregularity of the aortic wall have been regarded diagnostic of syphilitic aortitis by various observers.[15,26]

Our results with fluoroscopy have led us to believe that these signs are not pathognomonic of syphilitic aortitis. Two cases of local dilatation of the proximal portion of the aorta were observed; one in a syphilitic, the other in a non-syphilitic. O'Kane and his coworkers[20] observed local aortic dilatation in a few patients that proved to be due to arteriosclerosis at autopsy. This lesion has also been described in arterial hypertension, coarctation of the aorta, rheumatic aortic insufficiency and syphilitic aortitis.[19] In other words, it must be remembered that local aortic dilatation is suggestive but not pathognomonic of syphilitic aortitis. We missed the correct diagnosis in one instance because we failed to take this into consideration. This patient had a positive Wassermann reaction, signs of aortic insufficiency and Roentgen ray evidence of local dilatation of the aorta suggestive of beginning aneurysm. Autopsy, however, revealed a rheumatic lesion of the aortic and mitral valves and a normal aorta.

Our failure to identify early syphilitic aortitis roentgenographically has been noted previously by other authors.[1,14b] Various proposed measurements of the aorta to detect early syphilitic aortitis have proved to be unreliable ground for diagnosis leading to error.

Every reported radiologic abnormality of the syphilitic aorta including saccular aneurysm has been observed in non-syphilitic aortic disease. Although saccular aneurysm of the aorta is almost always the result of syphilis, it must be remembered that in rare instances this lesion may be due to advanced arteriosclerosis, particularly in aged individuals. In our study of 200 normal patients diffuse dilatation was not observed in a single case. In 200 syphilitic patients of approximately the same age diffuse aneurysmal dilatation occurred in 6 cases or in 3% of the series. Diffuse dilatation was also observed in a few non-syphilitic cases, but always in the presence of marked hypertension, rheumatic aortic insufficiency or in aged patients with obvious arteriosclerosis. Evidently, diffuse dilatation is the most reliable Roentgen ray sign of syphilitic infection of the aorta before the advent of saccular aneurysm, providing arterial hypertension, arteriosclerosis and rheumatic aortic insufficiency are first ruled out.

Since the roentgenologic diagnosis is largely dependent upon a marked increase in the size of the aorta, lesser degrees of aortitis are frequently unrecognized. In fact, one serious complication of aortitis may be present without any change in the size of the aorta, namely, stenosis or occlusion of the coronary ostia.[27]

II. Physical Examination. Increased pulsation in the suprasternal notch, a systolic aortic blow, an accentuated or tympanitic aortic second sound and retromanubrial dullness have been reported as signs of syphilitic aortitis. The presence or absence of each of these signs was noted by us in the physical examination of 200 syphilitic and 750 non-syphilitic patients with the aim of determining their value in the diagnosis of syphilitic aortitis.

A. The least reliable of all physical signs proved to be visible or palpable pulsation in the suprasternal notch. Prominent pulsation was present in 2 out of 6 cases with diffuse aortic dilatation and slight or absent in 4. The diminished pulsation of the diseased aorta has been observed by other workers.[26] On the other hand, we frequently obtained prominent pulsation in both syphilitic and non-syphilitic patients who showed no evidence of dilatation on roentgenologic examination.

B. Retromanubrial dullness proved to be of little value in the diagnosis of aortitis. We obtained this sign in many non-syphilitic patients, with and without arterial hypertension. In some of these cases the aorta proved to be dilated on Roentgen examination; others however were merely elongated.

The "silent" aneurysm without signs or symptoms is well known to clinicians. Of 6 cases of saccular aneurysm seen in the course of this study one was suspected on the basis of percussion; while 5 remained undiagnosed after physical examination. Kampmeier[12] recently analyzed the results of percussion in 566 cases of saccular aneurysm. He found abnormal dullness in 22.4% of the cases and absent in the remainder. Obviously, percussion is not a very reliable method of clinical diagnosis since abnormal dullness is often absent in the presence of a dilated aorta and present more frequently with arteriosclerosis or hypertension than with aortic syphilis.

C. A slight systolic aortic murmur occurred in 3 out of 200 syphilitic patients or in 1.5% of the series. Two of these had diffuse aneurysmal dilatation of the aorta, one a normal aorta. It is important to note that a systolic aortic murmur occurred in only 2 out of 6 syphilitic patients who presented diffuse aortic dilatation; 4 had normal heart sounds. Furthermore, we obtained an identical murmur in 2% of the normal control series.

White and Wise[31] have similarly pointed out that a loud aortic systolic murmur is not pathognomonic of aortic syphilis, but that it may occur with aortic dilatation not due to syphilis as well as with aortic stenosis of rheumatic or sclerotic origin. We agree with these observers that a systolic aortic murmur cannot be regarded as specific evidence of aortic syphilis.

D. The tympanitic aortic second sound has been regarded pathognomonic of aortic syphilis by some clinicians[18] and of no value in diagnosis by others.[31] (By a tympanitic or tambour aortic second sound is meant a change in the quality as well as an increase in the intensity of the heart sound, characterized by a hollow or drum-like sound.)

We believe that the tympanitic aortic second sound may be a clue to the correct diagnosis providing the general condition of the patient is carefully analyzed. We are certain that this sign may occur with arteriosclerosis or arterial hypertension as well as with syphilis. We obtained this sign in 5 (2.5%) of 200 syphilitic cases under 50 years of age without hypertension. On the other hand, this sign occurred only once in 500 normal cases of the same age period. Because this sign is rare in normal individuals[8] we believe that it is of diagnostic value providing arteriosclerosis, valvular heart disease and hypertension are first ruled out. The following case illustrates this point.

Case Report. A colored male of 49 complained of moderate pain in the left axilla and left lower back, unrelated to effort. This was of 1 year's duration. Physical examination revealed a single positive physical finding, a tympanitic aortic second sound. In the absence of increased arterial pressure this sign suggested the possibility of aortic disease. The blood Wassermann reaction was negative, but questioning yielded a history of a primary infection 20 years ago. The roentgenogram revealed diffuse aortic dilatation (Fig. 4). The patient received a therapeutic test consisting of 4 gm. of potassium iodide daily and bismuth at weekly intervals. The response to the therapeutic test was dramatic. At the end of a month the pain was much less and the Wassermann and Kahn reactions of the blood became strongly positive on several occasions.

Although the tympanitic aortic second sound may be of value in diagnosis, this finding alone cannot be accepted as unequivocal evidence of aortic syphilis. Upon finding this sign, we believe that a careful roentgenologic examination is indicated to determine the presence or absence of an aortic lesion. In the final analysis, uncomplicated syphilitic aortitis can be recognized only by roentgenologic study since there are no physical signs that are pathognomonic of this condition.

III. Electrocardiograms. Electrocardiographic studies[5,29] have failed to show any significant changes during or following the primary or secondary lesion, or any characteristic abnormalities in latent or tertiary syphilis.

We analyzed the electrocardiogram of 160 syphilitic patients. The interval between the chancre and the electrocardiographic study varied from 3 to 39 years with an average interval of 14.7 years.

The electrocardiogram rarely shows abnormalities in uncomplicated syphilitic aortitis. Of 160 syphilitic patients without demonstrable complications, 5 presented an abnormal tracing. These consisted of an absent Q_4 together with a positive T_4, a diphasic T_2, and a PR interval of 0.24 second respectively. It is well known that these changes are not pathognomonic of syphilitic aortitis. Six other syphilitic patients had an abnormal tracing, but chronic rheumatic heart disease was present in 1 and arterial hypertension in 5.

The electrocardiographic changes of cardiovascular syphilis de-

velop late in the disease and are relatively unimportant clinically. Such changes are generally due to aortic regurgitation or stenosis of the coronary orifice, and rarely, to gumma or myocarditis.[11] Changes in the ventricular complex were present in 5 out of 6 cases with aortic regurgitation in the present study.

A normal electrocardiogram, on the other hand, does not rule out cardiovascular syphilis. This occurred in 1 case with aortic regurgitation, in 3 patients with saccular aneurysm and in 3 patients with diffuse aortic dilatation.

In agreement with other workers[31] we note that auricular fibrillation is rare in patients with syphilis. In our study auricular fibrillation occurred in 1 out of 200 syphilitic patients without aortic insufficiency, saccular aneurysm or arterial hypertension. It is significant that this patient had wide aortic dilatation and cardiac symptoms. Auricular fibrillation also occurred in 1 patient with aortic insufficiency and saccular aneurysm. A third case of auricular fibrillation was seen in association with syphilitic aortic insufficiency and hyperthyroidism. In this patient the arrythmia subsided after a partial thyroidectomy. Evidently, auricular fibrillation is not only rare in patients with syphilis but, when present, is a manifestation of a cardiac complication, either syphilitic or non-syphilitic.

Discussion. In 1932 Moore, Danglade and Reisinger[18] established diagnostic criteria for uncomplicated syphilitic aortitis. These criteria were: "(1) teleroentgenographic and fluoroscopic evidence of aortic dilatation; (2) increased retromanubrial dullness; (3) a history of circulatory embarrassment; (4) a tympanitic, bell-like accentuation of the aortic second sound; (5) progressive cardiac failure; (6) substernal pain; (7) paroxysmal dyspnea."

We are convinced that these criteria are not diagnostic of uncomplicated syphilitic aortitis, but are characteristic of aortitis with serious complications. It appears that Moore and his coworkers used the term uncomplicated aortitis inconclusively. By uncomplicated aortitis they understood a "supra-valvular involvement of the aortic wall with or without diffuse dilatation, but without valvular insufficiency or saccular aneurysm." It is significant that these workers failed to consider the condition of the coronary vessels in subjects with cardiac symptoms who came to autopsy. This is particularly important since a well-recognized cause of cardiac failure is syphilitic involvement of the coronary orifice. Stenosis or occlusion of the coronary orifice has been found at autopsy in 10% to 35% of cases with syphilitic aortitis.[2,4,6,16,25] Careful pathologic studies have proved: 1, that uncomplicated syphilitic aortitis is symptomless; and 2, that cardiac symptoms in a syphilitic patient are due to complications of aortitis, *i. e.*, saccular aneurysm, valvular insufficiency or stenosis of the coronary orifice, or to some unrelated condition such as degenerative or rheumatic heart disease.[13,32]

Cardiac symptoms, abnormal physical signs or a dilated aorta may occur with syphilitic aortitis but these criteria are not pathognomonic of this disease. It is well known that the identical criteria occur far more frequently with degenerative cardiovascular disease. The history of syphilis or the presence of a positive serology does not mean that syphilis is necessarily an etiologic factor. Furthermore, syphilitic aortitis and degenerative heart disease may coexist with syphilis playing no rôle in the production of symptoms. Thus Perry and Langsam[21] recently found at autopsy a number of cases with syphilitic aortitis who died of hypertensive disease. It cannot be emphasized too strongly that no single sign or symptom is all-important in the diagnosis of syphilitic aortitis. The diagnosis must rest upon roentgenologic examination plus a careful analysis of the general condition of the patient.

This study supports the contention that a positive clinical diagnosis of early syphilitic aortitis is practically impossible. This study clearly shows that a reliable diagnosis cannot be made before wide dilatation of the aorta has occurred. We agree with White and Wise[31] that a positive diagnosis of cardiovascular syphilis can be made only when one or more of the following findings is present: 1, a saccular aneurysm of the aorta or innominate artery; 2, aortic regurgitation appearing for the first time in a middle-aged person with a positive serologic reaction for syphilis; or 3, a diffusely dilated aorta without aortic regurgitation or hypertension, past or present.

Summary. We have attempted to repeat previously emphasized methods of examination to determine their value in the diagnosis of early or uncomplicated syphilitic aortitis. Two hundred patients with syphilis and 200 patients as normal controls were used for this purpose. Our conclusions are as follows:

1. There is no single pathognomonic sign of early syphilitic aortitis discernible either by Roentgen ray, electrocardiogram or physical examination.

2. It is impossible at present to make a positive clinical diagnosis of early syphilitic aortitis.

3. Roentgen ray examination is a valuable aid in the diagnosis of late aortitis, at times being the first or only indication that such a condition exists.

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HISTOLOGIC KIDNEY CHANGES IN THE COMMON ACUTE INFECTIOUS DISEASES.

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The physician, attending cases of the common acute infectious diseases, frequently experiences concern about the possibility of a renal complication, particularly in the presence of albuminuria and cylindruria. Discussions of the actual pathologic findings in the kidneys in these diseases have appeared in the medical literature over the course of many years, but are widely scattered under many individual subject headings. It was thought, therefore, that a review of the renal histopathology of the more common acute infectious diseases might be of interest. In this article no attempt is made to survey the extensive literature. Its basis is the postmortem material of 9 years (1930 through 1938) at the Willard Parker Hospital.

There was no selection of cases except that some were ruled out because of doubtful diagnosis or multiplicity of infection. There were 58 cases of scarlet fever, 70 cases of diphtheria, 98 cases of measles, 62 cases of pertussis, 16 cases of meningococcic meningitis, and 9 cases of varicella. The number of cases of poliomyelitis reviewed was arbitrarily limited to 50. In the text and the table included in this report the incidence of each type of lesion is expressed as a percentage of the total number of cases of that disease that came to autopsy. Because there were so few cases of influenzal

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meningitis and varicella, the incidence was expressed as the absolute number of cases as well as percentage. The lesions are grouped as diffuse glomerular, tubular, interstitial and vascular.

TABLE 1.—HISTOLOGIC CHANGES IN THE KIDNEYS IN THE ACUTE CONTAGIOUS DISEASES.

Disease.	Number of cases.	Diffuse glomerular lesions, %		Tubular lesions, %				Interstitial lesions, %		Vascular lesions, %				Clinical data, %		
		Increased glomerular cellularity.	Glomerulonephritis.	Albuminous degeneration.	Hyaline-drop degeneration.	Necrosis of tubular epithelium.	Casts in tubules.	Interstitial infiltration.	Interstitial edema.	Focal embolic glomerulonephritis.	Glomerular thrombi.	Septic embolism.	Aseptic embolism.	Albuminuria.	Positive blood cultures (all types).	Hemolytic streptococci in blood.
Scarlet fever	58	6	3.4	95	9	7	46	77	42	3.4	0	3.4	1.7	69	79	63
Diphtheria	70	7	0	91	25	16	67	48	13	1.4	4.3	2.8	1.4	93	50	48
Measles	98	3	0	93	8	4	36	19	7	0	3	0	0	81	73	60
Pertussis	62	0	0	77	19	0	5	1.6	0	0	6.4	0	0	67	33	13
Poliomyelitis	50	0	0	68	4	0	18	0	4	0	0	0	0	53	30 (10 cases)	10
Meningococcic meningitis	16	0	0	94	0	0	19	6.2	43	0	0	0	0	50	50 (10 cases)	20
Influenzal meningitis	10	0	0	70	10	0	50	30	20	0	0	0	0	87.5 (8 cases)	37.5 (8 cases)	0
Varicella	9	0	0	89	11	0	22	0	0	0	0	0	0	75 (4 cases)	60 (5 cases)	60

GLOMERULAR LESIONS. Congestion of the glomeruli was very frequent. Droplets of protein matter were found in Bowman's capsule in most of those cases that showed degenerative tubular changes. Since the glomerular loops themselves were unchanged in these cases and there was no epithelial proliferation or desquamation, these changes were not regarded as inflammatory. Their incidence and significance appears to be about the same as toxic nephrotic changes, and they are not included in the table. The normal involutional obliteration and fibrosis of some glomeruli seen in infants and senile arteriosclerotic lesions were omitted as irrelevant.

The minimal glomerular lesion which may be regarded as inflammatory is listed as *increased glomerular cellularity*. Although this may be similar to the lesion referred to as "subclinical glomerulitis" by Bell,[1] no basement membrane staining was done nor any attempt made to distinguish between epithelium and endothelium, and we do not go beyond a descriptive term. This lesion is characterized by a marked increase in the cells of the wall of the glomerular tuft or in polymorphonuclears in the lumens of the loops. It will be noted from the table that these minimal glomerular lesions are infrequent.

A true *diffuse glomerulonephritis* was seen in only 2 cases of scarlet

fever (3.4% of the cases of that disease). In 1 case death occurred on the 28th day of the scarlet fever; in the other on the 22d day of the scarlet fever and the 12th day of the nephritis. The first showed swelling of all glomeruli which had anemic and very cellular loops filling the glomerular capsule. In numerous glomeruli of the second case the vascular tufts contained hyaline thrombi; epithelial crescents were present in many capsules; occasional small intracapsular hemorrhages were observed. Both cases had the clinical picture of glomerulonephritis.

Tubular Lesions. *Albuminous degeneration* (also called granular degeneration, and from its gross appearance, cloudy swelling) was the most frequent lesion of any type in all the diseases dealt with. In the mildest cases it was seen in the proximal convoluted tubule, especially in the straight part situated in the medullary rays. In severe cases the entire proximal and distal convoluted tubules were involved. In the table all cases showing albuminous degeneration are listed whether it was seen alone or with the more severe degenerative changes. It was seen with almost equal frequency in scarlet fever, diphtheria, measles and meningococcic meningitis, and somewhat less frequently in pertussis and poliomyelitis. Albuminous degeneration alone, without the more severe forms of degeneration or the first stage of nephrosis (Fahr[4]), was observed in 80% of scarlet fever, 65% of diphtheria, 85% of measles, 58% of pertussis, 64% of poliomyelitis, and 94% of meningococcic meningitis.

The appearance of *hyaline droplets* indicates the second stage of nephrosis according to Fahr. In our series, hyaline droplet degeneration was never diffuse and was usually seen in the subcapsular and mid-cortical layers, often in the neck of the proximal convoluted tubule. In a few cases it was observed in the epithelium covering the glomeruli. The total of hyaline droplet degeneration seen, with or without tubular necrosis, as listed in the table, was highest in diphtheria with 25%. Pertussis came next with 19%. The incidence in measles, scarlet fever and poliomyelitis was low, with 8%, 9%, and 4% respectively. Hyaline droplet degeneration without necrosis, that is, the second stage of nephrosis, was 14% in diphtheria, 19% in pertussis, 5% in measles and 4% in poliomyelitis.

Coagulation necrosis, which indicates the third stage of nephrosis (Fahr), was seen most frequently in diphtheria where it was present in 16%. Far fewer cases of scarlet fever (7%) and measles (4%) showed this change. It was not present in the other diseases. Coagulation necrosis of an occasional single cell was not counted. Those cases alone were listed under this heading where groups of entire cross-sections of tubules showed deeply eosinophilic cells with pyknotic nuclei or absence of nuclei. In diphtheria desquamation of these deeply eosinophilic (necrotic) cells was often accompanied by regeneration of low slightly basophilic cells. The necrosis was usually limited to a few groups of tubules. In only 1 case was

necrosis diffuse, resembling that of mercurial poisoning. No calcium deposit as seen in mercury poisoning or in diphtheria of the pre-antitoxin days (Reiche[6]) was noted.

Casts. The presence of casts in the tubules as seen in histologic sections was enumerated. The findings are listed under tubular changes for reasons mentioned in the discussion. Casts, usually hyaline, were found with striking frequency in diphtheria (67%), and much less often even in scarlet fever, the disease which came next with 46%.

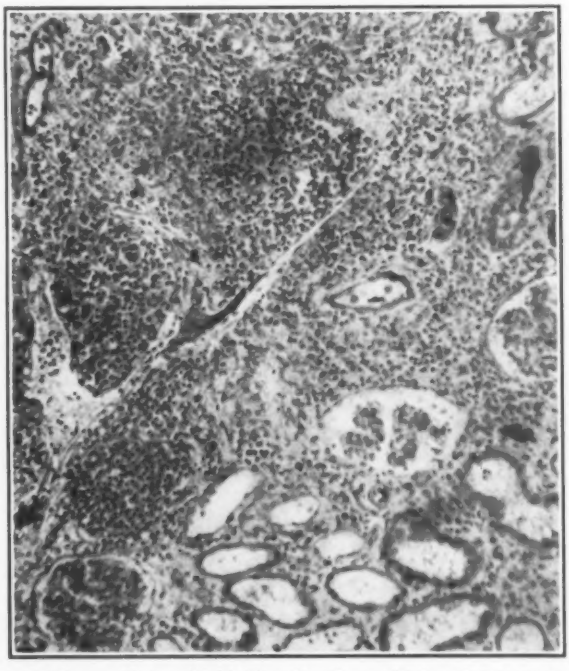

FIG. 1.—Scarlet fever. Interstitial infiltration (interstitial nephritis) (100 ×, slightly enlarged).

INTERSTITIAL LESIONS. These were an infiltration of inflammatory cells into the interstitial tissues and an inflammatory edema. They are listed separately, although both, probably, are parts of the same process (Kimmelstiel[5]).

The interstitial cellular exudate consisted chiefly of lymphocytes. Some large mononuclear and plasma cells were usually present. Small numbers of polymorphonuclears, including a few eosinophils, were found in scarlet fever. The infiltrates varied from small perivenous collections at the junction of the cortex and medulla to a diffuse, almost leukemoid, infiltration of both medulla and cortex.

Interstitial infiltration was seen most outstandingly in scarlet fever (77%) and in diphtheria (48%). In measles it was much less frequent (19%), and was negligible in other conditions.

The extent of the infiltration was estimated according to the scheme of Brody and Smith[2] wherein 1+ represents the perivascular collections; 2+ beginning infiltration into surrounding tissue, and 3+ and 4+ the more extensive and diffuse distribution. In scarlet fever 24% were of 3+ and 4+ degree; in diphtheria only 3% were of 3+ severity and none of 4+.

Interstitial edema, resulting in wider separation than normal, of the tubules in the cortex was also seen most commonly in scarlet fever (42%) where it was usually accompanied by interstitial cellular infiltration. It was less frequent in other diseases except in meningococcic meningitis where it was present in 43% of the relatively small series reviewed, with one-seventh of the cases showing cellular infiltration.

Vascular Lesions (aside from diffuse inflammatory glomerular lesions). *Focal embolic glomerulonephritis* or glomerular embolism was seen in 2 cases of scarlet fever (3.4%) and 1 case of diphtheria (1.4%). These were septic emboli of a small number of glomeruli. The sepsis in 1 case of scarlet fever was the result of an acute hemolytic streptococcic ulcerative endocarditis; in the other, the organism was a pneumococcus, lobar pneumonia having followed the scarlet fever. In this case focal embolic glomerulonephritis was superimposed on diffuse glomerulonephritis which was present for a few days before the onset of the pneumonia. The two lesions were unmistakably different. In the diphtheria case blood culture failed to show any growth.

Thrombosis of otherwise unchanged glomerular loops was noted in a few cases of diphtheria, measles, and pertussis. There was no cardiac valvular or other lesion in these cases which might be a possible source of emboli. The thrombi consisted of fibrin without bacteria, the glomerular loops showed no necrosis or increased cellularity. No polymorphonuclears were seen in the capillaries or in the capsules; nor was any blood or epithelial crescent formation present in Bowman's capsules. The thrombosis affected a few or many glomeruli in one or both kidneys. Some of the kidneys showing this change were otherwise of surprisingly normal appearance and others showed degenerative changes in the tubules. In a few cases blood chemistry and urinalysis done shortly before death were found to be normal. Because of the negative findings these 9 cases could not be listed as focal glomerulonephritis. The cases occurred in children under 2 years of age. The significance or duration of the lesion could not be determined. They may be terminal.

Several cases of *embolic lesions*, either septic or aseptic, affecting renal blood vessels *other* than the glomerular tufts were seen in scarlet fever and in diphtheria. Aseptic embolism of the larger

branches of the renal artery arising from aseptic mural thrombi of the left ventricle was seen in a case of scarlet fever which presented also embolism of the popliteal artery, and in a case of diphtheria with embolism of the femoral artery and anemic infarcts of the spleen. Septic embolism of interstitial capillaries without focal embolic glomerulonephritis was seen in 1 case each of scarlet fever and diphtheria. Periarteritis nodosa involving most of the abdominal organs and the heart was seen in a woman of 27, who developed hematuria, albuminuria and nitrogen retention 3 weeks after the onset of scarlet fever. She died, anuric, 6 weeks after the beginning of the scarlet fever.*

FIG. 2.—Diphtheria. Bland thromboses without necrosis or inflammation in the glomerular tufts (100 ×).

CLINICAL LABORATORY DATA. Urinalysis was available in one-third to one-half of the cases. It was absent in most cases with a short stay in the hospital, as, for example, cases of poliomyelitis admitted in a dying state, and in many baby girls. The proportion of severe albuminuria (2+ to 4+) was highest in diphtheria by far, next most frequent in scarlet fever. Most of the severe cases of albuminuria showed moderate numbers of white cells and casts. Red cells were rarely present and then in a relatively small number.

It was thought that the incidence of bacteremia in relation to the extent and severity of renal changes might be of interest; and par-

* Case to be reported by V. B. Dolgopol.

ticularly hemolytic streptococcic septicemia in reference to interstitial nephritis. It is seen that the highest percentage of positive blood cultures occurs in scarlet fever (79%) and in measles (73%). In both of these four-fifths of the positive cultures were of hemolytic streptococci. Other bacteria grown were *Streptococcus viridans*, pneumococcus, meningococcus and diphtheria bacillus.

Discussion. It will be noted that in this series diffuse glomerulonephritis was rare. It was seen only in scarlet fever, and there only in 3.4% of the cases (2 cases). Estimates as to the clinical occurrence of glomerulonephritis following scarlet fever vary widely but it should be pointed out that most deaths following scarlet fever occur before the third week when nephritis is most likely to occur; and that in only a small percentage of cases is acute glomerulonephritis a cause *per se* of death. Cases dying subsequently of the chronic effects of glomerulonephritis would not, of course, be seen in a hospital for acute infectious diseases. In discussing the pathogenesis of acute diffuse glomerulonephritis Bell[1] describes a proliferation of the glomerular capillary endothelium of varying severity occurring in the course of many infectious diseases, notably in subacute bacterial endocarditis and puerperal sepsis. He calls this lesion "subclinical glomerulitis." When the proliferation is of such intensity that the capillary lumens are blocked, clinical acute glomerulonephritis appears, according to Bell. Thus he believes acute glomerulonephritis and subclinical glomerulitis are continuous and essentially a matter of degree. As mentioned before, actual epithelial-endothelial ratios were not determined in our study. The mere impression of an increased number of nuclei in the glomeruli was noted as "increased glomerular cellularity." Thus whether it is even the same process Bell describes we cannot say. However, in a small number of cases of scarlet fever in Bell's series there was no endothelial proliferation, and in our cases "the increased glomerular cellularity" was not more frequent in scarlet fever than in diphtheria. Consequently we cannot make any inferences as to the significance of the increase in glomerular cellularity or its relation, if any, to glomerulonephritis. In 4 cases with "increased glomerular cellularity" in which urinalysis was available 2 showed albumin and 2 were negative.

Tubular degeneration (toxic nephrosis of Fahr[4]) is the most frequent kidney lesion observed in the infectious diseases. The milder variety (albuminous degeneration) was observed with almost equal frequency in scarlet fever, diphtheria and measles. The more severe varieties (hyaline droplet degeneration and necrosis of tubular epithelium) were more frequent in diphtheria and this coincides with the higher incidence of albuminuria in diphtheria. Of course, cases seen at autopsy would be expected to show the most severe generalized septic and toxic changes; clinically, in non-fatal cases, these histologic changes probably occur far less frequently as estimated by albuminuria, cylindruria, and so on.

It should be mentioned that, since septic complications were the usual cause of death in scarlet fever, a pneumonic complication in measles and pertussis, the changes recorded of a toxic nature must to a considerable extent be attributed to the superimposed infection. However, the severity and frequency of the degenerative lesions in diphtheria far exceed those in other conditions and are as striking as the inflammatory lesions in scarlet fever. While the effects in diphtheria were undoubtedly chiefly the result of the toxin of *C. diphtheriæ*, almost one-half the cases had a hemolytic streptococcic sepsis and the findings must be interpreted in the light of this also.

The occurrence of casts in the urine or in the tubules in kidney sections is generally associated with albuminuria. Albuminuria is usually taken to indicate leakage of plasma protein through the glomerular tuft. The fact that, histologically, the glomeruli may appear normal in the presence of severe albuminuria cannot, of course, be used as an argument against a functional derangement of the glomeruli. However, the anatomic tubular injury is so prominent in diphtheria and the parallelism of tubular injury, casts in tubules, and albuminuria so evident in this series as to suggest a significant relationship between the tubular degeneration and the casts. We have, therefore, listed "casts in tubules" as a tubular lesion. This is also convenient for the mere fact that casts are actually seen in the tubules whatever the nature of their origin.

Interstitial nephritis was observed most commonly in scarlet fever and no other condition approached it in the severity of these changes. The percentage of hemolytic streptococcus sepsis was approximately the same in measles as in scarlet fever but interstitial nephritis was much less common in measles and of a milder degree. In diphtheria, although the incidence of streptococcic sepsis and interstitial nephritis was parallel, the changes again were of a much milder degree. Thus, while the argument for the relationship of streptococcic sepsis, in general, and interstitial nephritis is strong, there would appear to be a particularly violent and frequent reaction in scarlet fever. Kimmelstiel[5] states that this lesion is usually found at autopsy without any history of a disturbance of renal function. He describes 6 cases of anuria with azotemia in infections, burns and other diseases which showed interstitial nephritis at autopsy. However, he concludes that the anuria was not proved to be of renal origin and, in any event, may be merely coincident with the anatomic renal lesion and have no causal relationship. He found the lesion present in various types of hemolytic reactions, especially following blood transfusions, and in liver disease or injury —the so-called hepatorenal syndrome. He regards the lesion as an anaphylactoid or hyperergic response to foreign protein or protein split-products, and not specifically a reaction to streptococcic toxins, as do Brody and Smith.[2]

No attempt at clinico-pathologic correlation in cases of interstitial nephritis was made here beyond comparison of the presence and

severity of albuminuria and of the histologic lesion. No parallelism was found. The severest grades of interstitial nephritis were often accompanied by little or no albuminuria, and many 3+ and 4+ albuminurias occurred in the absence of the lesion.

The bland thromboses of individual glomerular loops without necrosis or inflammation found in a few cases were of uncertain significance or duration. It was felt that they might represent a terminal process associated with stagnation of blood. The otherwise normal appearance of the thrombosed loop argued against an embolic or a septic thrombotic process, either one of which may be the mode of origin of actual focal embolic glomerulonephritis. The latter lesion was seen in a few cases in this series and was very different.

The embolic interstitial lesion seen, septic and aseptic, differed in no way from those not associated with an infectious disease.

The occurrence of periarteritis nodosa after scarlet fever is mentioned by Friedberg and Gross.[4]

Rather conspicuous by its absence in this series is suppurative pyelonephritis. Despite the presence of moderate numbers of white cells, along with albumin and casts in the urine, in many cases, especially of diphtheria, no suppurative lesion was found in the kidneys. It should be recognized that these urinary findings in the acute infectious diseases may be the result of toxic injury to the kidney and do not necessarily indicate suppuration of the urinary excretory tract.

Summary. Acute diffuse glomerulonephritis is rare in cases of the common acute infectious diseases coming to autopsy. It was present only in 3.4% of scarlet fever and in no other disease.

Tubular degeneration is the most frequent lesion in the kidney in all the acute infectious diseases. The more severe degenerative changes are most frequent in diphtheria. Hyaline droplet degeneration was present in 25%, epithelial necrosis in 16% of cases of diphtheria.

Interstitial nephritis occurs most often in scarlet fever (77%). Interstitial nephritis and streptococcic hemolytic sepsis are parallel in scarlet fever and diphtheria but not in measles where streptococcic sepsis is three times as frequent as the nephritis.

Pyelonephritis was not found in this series.

Albuminuria was very frequent in all diseases.

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ACUTE PORPHYRIA.*

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The porphyrias may be classified as congenital and acute porphyrias, and the acute porphyrias may be classified further as acute toxic porphyria and acute idiopathic porphyria.[4b,9,12] Excellent reviews of the subject have appeared during recent years[3,9,16a,b,17,18] and it would seem that the number of patients who have acute porphyria is increasing comparatively rapidly. This may well be accounted for by the fact that physicians are becoming better acquainted with this disease and are more on the alert to recognize a case when it is presented to them. Up to 1939 fewer than 30 cases of congenital porphyria had appeared in the literature, about 100 cases of acute toxic porphyria and 153 cases of acute idiopathic porphyria.[3,16] Several additional cases of acute porphyria have been published recently[5,7,8,10,15] but the number of cases of congenital porphyria in the literature has not been augmented.

It has been pointed out frequently[9,18] that the acute toxic forms and the acute idiopathic forms of porphyria are indistinguishable, either clinically or by laboratory methods. The acute toxic form of porphyria is recognized only on the basis of the presence of a toxic agent which apparently is an etiologic factor. Eldahl[4a] claimed that there are other precipitating factors such as anxiety, exhaustion and infection.

Acute porphyria[9,18] of either type is characterized by gastrointestinal disturbances and involvement of the central nervous system. There may or may not be fever. Commonly there is severe abdominal pain which may be generalized or which may be confined to the lower part of the abdomen. There may be nausea, vomiting, constipation and ileus; in addition there may be mild jaundice. There is occasionally a diffuse or spotted pigmentation of the skin, but not of the mucosa, the nature of which is unknown. Involvement of the central nervous system is exhibited most frequently by an ascending (Landry) type of paralysis, and death is frequently due to bulbar involvement with respiratory failure. There are frequently delirium and hallucinations. Photosensitivity occurs rarely in acute porphyria. Pathologic changes in the central nervous system at necropsy have been reviewed extensively.[9]

* Abridged portion of thesis submitted by Dr. Nesbitt to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Ph.D. in Medicine.

Schulte studied patients who had acute toxic porphyria and expressed the belief that the disease is due to the action of the toxic agent. His work and the work of others convinced Mason and associates that the toxic agent, usually a barbiturate, in some manner produces the disease and that a constitutional liability need not necessarily be assumed in every instance, it being reasonable to assume that acute toxic and acute idiopathic porphyrias are caused by some endogenous or exogenous intoxication which affects certain persons who may have an idiosyncrasy to certain drugs. It might be assumed, of course, that there is always some toxic agent involved as an etiologic factor but that in cases of acute idiopathic porphyria the toxic agent remains unrecognized. Support for such an assumption might be interpreted from a report by Weiss[20] of 2 patients in whom acute idiopathic porphyria developed, 1 of the patients having replaced the initial patient in the capacity of cook in a particular restaurant.

Günther,[6] who first described the porphyrias, expressed the opinion that the disease in all instances represents a constitutional anomaly of pigment metabolism. Subsequent work, especially those case reports which indicate that the porphyrias are a familial disease, has done much to confirm Günther's original idea. Families have been observed in which more than one member was afflicted with the manifestations which are considered to be characteristic of acute porphyria; in a few instances one member of the family suffered from acute porphyria while another member of the same family suffered from congenital porphyria.[18] Barker and Estes[2] early reported a very remarkable instance in which two sisters died of acute idiopathic porphyria while a third sister, the mother and maternal grandmother presented histories of abdominal colic, accompanied by constipation, vomiting and the voiding of very dark urine. Waldenström[16a] described many such families in which often both the acute toxic and the acute idiopathic forms may occur in the same family, and he claimed that the disease is inherited and transmitted as a dominant Mendelian characteristic. Turner demonstrated that the error in metabolism is not limited to the periods of acute symptoms in these patients, but that they may excrete uroporphyrin and its metal complex between such episodes. In acute toxic porphyria a definite precipitating factor is apparent to explain the acute episodes, but the cause of such episodes in acute idiopathic porphyria remains obscure.

The diagnosis of acute porphyria of either type depends on an evaluation of the clinical picture and must be confirmed by an examination of the urine. At one time it was believed that the demonstration of uroporphyrin in the urine of such patients was necessary to establish the diagnosis,[16a] but several cases of porphyria have been reported in which uroporphyrin was not excreted in the urine[1,11,12] but other characteristic pigments were present. Usually

patients who have acute porphyria excrete uroporphyrins III and I in the urine with a great predominance of the Type III isomer. Uroporphyrin has not been demonstrated in the feces of such patients, which usually contain only a small amount of coproporphyrin III. It has been shown recently that uroporphyrin may be excreted as a metal complex[3,14] and between the acute episodes the fraction of uroporphyrin which is present as a metal complex may be increased. Usually only a relatively small amount of coproporphyrin III is present in the urine.[14] Waldenström,[16b] and Waldenström and Vahlquist described in the urine of such patients the presence of a "porphobilinogen" which on standing or on adding acid and boiling is converted into uroporphyrin III and a very little amount of uroporphyrin I. It is becoming more and more evident that other pigments are involved in this metabolic disorder. Pigments other than porphyrins may account for most or all of the dark color of the urine of these patients. Turner expressed the opinion that urofuscin accounted for most of the color in the urine of such a patient which he investigated. Waldenström and Vahlquist expressed the belief that pigments made up of several united pyrrol nuclei may be present in such urine while other workers claim that urofuscin, skatol red or urobilin may constitute most of the color of the urine.

Case Reports. CASE 1.—The patient, a 34-year-old American-born man, employed as a clerk, always had enjoyed excellent health and never had observed anything unusual about the color of his urine. Seven months before coming to the Mayo Clinic he had had a carious impacted third molar tooth removed. An infection occurred in the tooth socket which was sufficiently severe to warrant hospitalization and he was given sulfanilamide. During the first 36 hours 100 gr. (6.5 gm.) of sulfanilamide was administered, but then the drug was discontinued because of the onset of severe, generalized abdominal pain, cramps and ileus, and it was observed that the patient's urine was the color of grape juice although it did not contain blood. The abdominal pain and red urine persisted and 10 days later the onset of generalized paresthesia, consisting of a burning, scalding sensation, was noted over the face and body. Six weeks later the patient's gait became shuffling until he could not walk because of the gradual onset of paralysis of his legs and then of his arms. He became incontinent of urine and feces and an indwelling catheter was used. During this time he acquired a chronic urinary infection. For 6 or 8 weeks he experienced transient episodes of delirium and hallucinations and during much of this time he had to be fed through a tube. Three months before coming to the clinic he first noted some return of function in that he could move his toes, and within 2 months he could shuffle along unaided. Gradually his sphincteral control of urine and feces returned. Frequently throughout this period his urine would be dark red for several days at a time. He had lost 50 pounds (22.7 kg.) during the illness.

The patient's family history was interesting in that his mother had died during an illness similar to that of the patient. She had suffered from severe abdominal cramps and paralysis and had voided very dark red urine.

Physical examination revealed an emaciated, gaunt young man who had great difficulty in progressing by means of a shuffling gait. The blood pressure was 120 mm. of mercury systolic and 80 diastolic. The pulse

rate was 104 and the temperature by mouth 98.6° F. There were marked and symmetrical weakness of the lower extremities which was graded −3 to −4 (on the basis of 1 to 4) and symmetrical weakness of the shoulder girdle and upper extremities which was graded −2 to −3. There were also marked atrophy and loss of muscle tone over these distributions. The biceps, triceps and patellar reflexes were absent bilaterally. The Achilles reflexes were present and about equal. No Babinski or Hoffman reflex was present. There were no sensory changes apart from hyperesthesia which was present over both the upper and lower extremities. It was noted that the paralysis was more nearly a radicular type than a peripheral paralysis and that from the history of delirium and of loss of sphincteral control there must have been involvement of the cerebrum and spinal cord.

Laboratory Studies. The concentration of hemoglobin was 14 gm. per 100 cc. of blood; the erythrocytes numbered 5,200,000 and the leukocytes 7500 per c.mm. of blood. The percentages of the various types of leukocytes were as follows: lymphocytes 30.4, monocytes 1.5, neutrophils 65, eosinophils 2, and basophils 1. There were hyaline casts grade 2 in the urine and pyuria was graded 2 (on a basis of 1 to 4 in which 1 indicates the least and 4 the greatest concentration). Culture revealed *Escherichia coli*. Excretion of sulphonephthalein was 25%. The flocculation reaction for syphilis was negative. The concentration of urea was 48 mg. per 100 cc. of blood, the concentration of bilirubin was 1 mg. per 100 cc. of serum with an indirect van den Bergh reaction and the sedimentation rate was 8 mm. per hour. Liver function test (bromsulphalein) did not show dye retention. Roentgenographic examination of the chest gave negative results.

The amount of coproporphyrin excreted in the urine of this patient was determined each day both in the fresh specimen and in the urine after it had remained exposed to the air and sunlight for several hours. The fresh urine was brownish red but became a little darker on standing. These results are represented in Table 1. From the pooled urine collections 0.64 mg. of uroporphyrin III was isolated and identified, the melting point of the methyl ester being 260° C. An amount of uroporphyrin I (too small to weigh) was isolated, the melting point of its methyl ester being 301° C.

TABLE 1.—EXCRETION OF ETHER-SOLUBLE PORPHYRIN IN THE URINE (CASE 1).

Day.	Volume of urine, cc.	Coproporphyrin, micrograms per 100 cc. in 24-hr. specimen.		Nicotinic acid, mg. per day.
		Fresh urine.	After standing.	
1	1425	952	1454	0
2	1065	614	964	0
3	685	345	543	0
4	1095	552	867	0
5	1205	716	1125	100
6	660	196	307	150
7	680	428	672	300
8	1095	283	445	300
10 months later	1800	0	299	0

A small amount (too little to weigh) of coproporphyrin III was isolated, the melting point of its methyl ester being 143° C.; no coproporphyrin I was isolated from the urine. It was demonstrated that the zinc metal complex of uroporphyrin was present in this urine. The native urine exhibited the two typical absorption bands of the metal complex at 577 and 541 millimicrons. On the addition of a few drops of concentrated hydrochloric acid to the urine in the cuvette these bands promptly disappeared and were replaced by the bands of uroporphyrin. On long standing, deep brown crystals in beautiful rosettes separated from the urine from which porphyrins had been removed. These crystals did not melt up to

300° C. and they were insoluble in the usual organic solvents, including ether, acetone, chloroform, carbon tetrachloride, methyl alcohol, amyl alcohol and 25% hydrochloric acid. The nature of this substance is as yet to be determined.

CASE 2.*—The patient, a 33-year-old housewife, had been underweight and chronically fatigued. There was nothing to suggest porphyria in other members of the family. During the past 3 years she had experienced 9 episodes characterized by cramping pains in the right lower part of the abdomen and in the midabdomen, often so severe that morphine did not relieve them. There was usually some epigastric distress, nausea and vomiting with these attacks, which lasted from a few days to several weeks. During these episodes the patient usually became depressed mentally, expressed a feeling of impending death, and would become so irrational as to suggest the possibility of encephalitis. On several of these occasions it was observed that her urine was strikingly dark and red like port wine.

One month after the most recent episode, at the patient's urgent request, operation was performed. At this time the physical examination gave essentially negative results. The urine was straw-colored and did not show any abnormalities with the usual tests. The erythrocytes numbered 4,050,000 per c.mm. of blood and the leukocytes 8200. The concentration of hemoglobin was 12 gm. per 100 cc. of blood. The percentages of the various types of leukocytes were as follows: neutrophils 60, lymphocytes 36, mononuclears 2 and eosinophils 2. Operation consisted of removal of a right ovarian cyst the size of an olive, appendectomy and uterine suspension.

Four days after operation the patient began to menstruate and complained of severe pains in the lower part of her abdomen which did not abate in severity following cessation of the menstrual flow. Her temperature rose to 102° F. The abdominal pains became more severe and the patient became apathetic and felt that she was going to die; it was observed that her urine had become dark red. She became increasingly confused mentally and complained of a tight, choking sensation in her throat. She also complained that her tongue felt thick and her speech was not clear. She experienced respiratory distress and an inability to get air into the lungs although there was no evidence of pulmonary edema. Her respirations became labored and shallow and she expired on the seventeenth postoperative day, apparently from bulbar paralysis, despite supportive measures which included the use of oxygen.

A 400-cc. specimen of this patient's urine† was received for examination. The urine was very dark red brown. It was found to contain 1.057 micrograms of ether-soluble porphyrin per cc. of urine. It was further demonstrated by means of the method which has been described recently by Watson[19] that coproporphyrin III comprised 88% of this porphyrin, the remainder being coproporphyrin I. From this single specimen of urine 0.621 mg. of uroporphyrin III was isolated as the methyl ester, melting point 270° C. A small amount (too little to weigh) of uroporphyrin I was isolated, the melting point of the methyl ester being 301° C. Spectroscopic examination of the native urine revealed that the uroporphyrin was present as the zinc metal complex.

CASE 3.—The patient, a 51-year-old American-born housewife, complained of repeated attacks of dysphagia, abdominal bloating and profound weakness, during which periods her urine had been observed to be extremely

* Dr. C. J. Watson, of the University of Minnesota, also has investigated this case including a study of feces and urine as well as blood, kidneys and liver obtained at necropsy.

† We are indebted to Dr. C. E. Lynn of Dubuque, Iowa, for having furnished us the account of this patient's illness as well as having furnished us with the urine specimen for examination.

dark red. The family history was not remarkable and the patient's past history presented only the story of a chronic duodenal ulcer. Two years previously on two occasions she had observed that her urine suddenly became very dark red and stayed so for approximately 10 days, during which time she complained only of some fatigue and weakness and noticed that her skin appeared to become a little yellow. During the year before coming to the clinic she had experienced approximately 8 episodes lasting from 2 or 3 days to several weeks which were initiated and characterized throughout by the very dark red color of her urine. During these periods she complained principally of dysphagia, and that cold and solid foods seemed to stick beneath the sternum before entering the stomach. She also experienced profound weakness, abdominal bloating, and dyspnea on exertion, and her skin appeared to become somewhat yellow. At such times she always had been found to be anemic, and on several occasions had required repeated blood transfusions. During several of these attacks she had exhibited psychotic manifestations which suggested a paranoid trend.

On examination she was somewhat undernourished and pale and there was questionable jaundice. Otherwise there were no findings of note. Special examination of the central nervous system was carried out but with negative results.

Laboratory Studies. The concentration of hemoglobin was 10.1 gm. per 100 cc. of blood; the erythrocytes numbered 2,970,000 per c.mm. of blood and the leukocytes 10,500. A blood smear revealed a macrocytic type of anemia. The routine flocculation tests for syphilis gave negative results. The urine was acid in reaction and its specific gravity was 1.019. Albuminuria was graded +3 (sulphosalicylic method). Pyuria and erythrocyturia were each graded 1 (on a basis of 1 to 4) and granular casts were graded 4. The basal metabolic rate was +2%. The percentages of the various types of leukocytes were as follows: lymphocytes 39.5, monocytes 3.5, neutrophilic leukocytes 56, eosinophils 0.5, and basophils 0.5. There were 256,000 platelets per c.mm. of blood. The Donath-Landsteiner reaction for autohemolysins was negative. Erythrocyte fragility was within the normal range and the time for clot retraction was normal. The concentration of urea ranged from 20 to 82 mg. per 100 cc. of blood, the concentration of creatine was 1.5 mg. per 100 cc. of blood and the concentration of sulphates was 8.8 mg. per 100 cc. of serum. The concentration of bilirubin was 1.8 mg. per 100 cc. of serum and the van den Bergh reaction was indirect. The concentration of proteins was 6.3 gm. per 100 cc. of serum with an albumin-globulin ratio of 3.5/1. A fasting concentration of sugar was 94 mg. per 100 cc. of blood. A catheterized specimen of urine showed no growth of organisms. Repeated spectroscopic examination of the urine revealed the presence of porphyrin which was not identified further and also of oxyhemoglobin. Roentgenographic examinations of the chest, esophagus, colon and terminal portion of the ileum gave negative results. Evidence of a duodenal ulcer was visualized.

While in the hospital under observation the patient exhibited several episodes as previously described during which times her urine, otherwise normal in appearance, became very dark brown or reddish-brown. It was believed that she had paroxysmal hemoglobinuria with nephritis and renal insufficiency. Considerable thought had been given to the possibility of porphyria. On her return to her home her condition remained much the same, the attacks becoming more frequent and more severe. Treatment consisted of Roentgen and radium therapy over the splenic area and moccasin venom, as well as iron by mouth and injection of liver extract.

Eighteen months after her first visit the patient again returned to the clinic where she remained under observation for a period of 1 month. She continued to have attacks just as before, although she now complained of considerable pain in the epigastrium and left upper quadrant during the

attacks. During the times between these episodes she felt perfectly well except for some weakness after each attack. The results of physical examination and laboratory findings were essentially the same as at the time of her initial visit. Cold tests by means of immersing the patient's limbs in cold water at 10° to 12° C. for a period of 1 hour failed to precipitate an attack or to produce hemolysis. The amount of ether-soluble porphyrin excreted daily in the urine and feces was within normal limits, ranging from 19 to 41 micrograms and 193 to 458 micrograms respectively. Spectroscopic examination of the blood showed the absorption bands which are characteristic of oxyhemoglobin. The concentration of bilirubin ranged from 1.6 to 2.4 mg. per 100 cc. of serum with an indirect reaction. A liver function test (bromsulphalein) showed no dye retention. The concentration of protein was 7.5 gm. per 100 cc. of serum with an albumin-globulin ratio of 1.1/1.

After leaving the clinic the patient's condition remained much the same, being characterized by frequent episodes of dysphagia, weakness, dyspnea, severe abdominal pains and mental depression, and during such times her urine was extremely dark red or brown. She expired 5 years after her first visit to the clinic and her local physician has given us an account of the terminal event and submitted necropsy material for our examination. The patient had cystitis and complained of constant nausea and vomiting and distress in the lower part of the abdomen. She was deeply jaundiced and the stools were clay-colored. The liver was palpable and there was considerable tenderness in the right upper quadrant of the abdomen. There was severe achromic anemia, the hemoglobin being 35%. She died rather suddenly, apparently from what was believed to be an acute cardiorespiratory collapse. The impression was that the patient had died of acute hepatic degeneration of unknown cause.

*Necropsy.** The lungs were described as being bronzed in appearance. The serum draining from clotted blood contained within the heart was of a bright, clear cherry color. The liver showed mild passive congestion; obstruction of the continuity of the bile passages could not be demonstrated. The spleen was increased in size and was rather firm. The kidneys showed evidence of considerable chronic damage and the entire kidney substance was of a deep bronze color.

Sections were prepared at the clinic for histologic examination† which included liver, spleen, bone marrow and kidney. There was much central necrosis of the liver cells. In some regions the necrosis was accompanied by an increase in the number of neutrophils. Many of the liver cells contained an increased amount of brownish-yellow pigment. In the spleen there was active proliferation of reticular cells with occasional mitotic figures and large multinucleated cells. There was hyaline fibrinoid change in the reticular cells of some of the Malpighian bodies. The bone marrow appeared hyperplastic but it was difficult to determine which cells were involved in the hyperplasia. Normoblasts were numerous. There was pyelonephritis with beginning abscess formation. Unusual findings were peculiar red casts which filled many of the renal tubules and the large amount of iron which was present in the epithelial cells.

Case 4.—The patient, a 20-year-old single, American-born woman, had enjoyed good health until 3 years before coming to the clinic when she had noticed some pruritus of the exposed portions of the body, including the face and hands, followed by a mild vesicular eruption. She continued to have this sort of difficulty periodically and had noticed that the onset of the dermatitis seemed to be related to exposure to sunlight. These attacks

* We are indebted to Drs. W. H. Barrow and H. A. Ball, San Diego, Calif., who furnished the clinical account of the patient's terminal illness and a description of the necropsy which was performed, as well as the tissues which we examined.

† We are indebted to Dr. A. H. Baggenstoss for this histologic study.

increased in severity and on several occasions she had had severe bullous lesions over her face, hands and ankles. Seven months before coming to the clinic the patient had complained of severe abdominal pain, nausea and vomiting and at that time her appendix had been removed. During that period it is to be noted that she exhibited mild psychotic behavior. The abdominal pain returned soon after operation and persisted until she came to the clinic. This pain was so severe that it doubled her up, was of a cramp-like nature and was rather diffuse about the region of the umbilicus.

Physical examination revealed much scarring with some pigmentation of the face, wrists and ankles, where the patient formerly had had her skin eruption. There was rather diffuse tenderness of the abdomen with no localizing features.

The urine was observed to be reddish-brown and contained some granular casts and a few pus cells. The concentration of hemoglobin was 14.2 gm. per 100 cc. of blood; the erythrocytes numbered 4,710,000 and leukocytes 8500 in each c.mm. of blood. The percentages of the various types of leukocytes were as follows: lymphocytes 32.5, monocytes 6.5, neutrophils 56.5, eosinophils 3.5, and basophils 1. Examination of the blood smear showed nothing of significance. Routine flocculation tests for syphilis gave negative results. The erythrocyte sedimentation rate was 43 mm. per hour. Culture of the urine showed no growth. The concentration of urea was 54 mg. per 100 cc. of blood and the concentration of chlorides was 476 mg. per 100 cc. of plasma. The concentration of bilirubin was 1.8 mg. per 100 cc. of serum on admission and the van den Bergh reaction was direct. The concentration of proteins was 8 gm. per 100 cc. of serum with an albumin-globulin ratio of 1.1/1. Roentgenographic examination of the chest gave negative results and a simple roentgenogram of the abdomen was negative. The urine was demonstrated to contain large amounts of coproporphyrin and uroporphyrin and it was demonstrated spectroscopically that the uroporphyrin was present as the zinc metal complex. The blood serum contained sufficient porphyrin to fluoresce in ultraviolet light; at least some of the porphyrin was ether-soluble. Light tests for photosensitivity were carried out and it was found that the patient was sensitive to the far ultraviolet part of the spectrum but, more particularly, to the red portion of the spectrum, which produced large urticarial lesions with severe pruritus.

The patient continued to complain of severe abdominal pain. She could not retain anything by mouth and vomited continually. The concentration of bilirubin became elevated to 19.8 mg. per 100 cc. of serum and the van den Bergh reaction was direct. The Quick prothrombin time became elevated from 23 seconds (normal, 20 seconds) to as high as 29 seconds.

Treatment consisted of the intravenous administration of 5% glucose in physiologic saline solution to which was added thiamin chloride and nicotinic acid. Liver extract was also administered intramuscularly. A feeding formula was employed; the food was administered by duodenal tube. The patient gradually improved. However, at the time of her dismissal the concentration of bilirubin was 17.6 mg. per 100 cc. of serum and the van den Bergh reaction was direct. Since she left the hospital her jaundice has cleared and she has complained only of considerable pruritus of the face. A detailed account of this case is to be published, including laboratory findings and tests for photosensitivity.

Comment. Three cases of acute porphyria (Cases 1, 2 and 4) have been described in which the diagnosis was confirmed by the demonstration of large quantities of uroporphyrin in the urine, most of which was of isomeric series III, there being a small fraction only of uroporphyrin I. It was shown by spectroscopic examination that this occurred as the zinc metal complex. Another case has

been described (Case 3) which presented the usual clinical picture of acute porphyria but which was diagnosed as paroxysmal hemoglobinuria on the basis of spectroscopic studies which demonstrated the presence of oxyhemoglobin in both the urine and blood serum during crises. It is suggested that this case actually represents a case of acute porphyria, and that the absorption bands which were observed and believed to be those of oxyhemoglobin were probably those bands of the zinc metal complex of uroporphyrin. The error might be explained easily since oxyhemoglobin produces absorption bands at 585 to 567 millimicrons and 550.7 to 527 millimicrons with maximal absorption which corresponds almost precisely with the bands of uroporphyrin zinc metal complex at 577 and 541 millimicrons respectively. The bands of the uroporphyrin zinc metal complex are distinguished only by the fact that, when a little concentrated hydrochloric acid is added, the metal complex is broken up and the bands are replaced immediately by the bands of uroporphyrin. Unfortunately no urine was procurable from this patient at the time of the present investigation which would have made it possible to make the differentiation one way or the other.

Case 1 is interesting because of the family history which would indicate that acute porphyria is just as much a familial disease as is congenital porphyria and that the underlying mechanism is an inborn error of metabolism, as originally suggested by Günther. This patient had taken sulfanilamide just antecedent to his illness, and it is possible that this may have acted as a precipitating toxic factor. His urine was shown to contain the zinc metal complex of uroporphyrin as well as unusually large quantities of coproporphyrin nearly a year after his acute illness and when he had shown considerable improvement. While under observation it could not be demonstrated that fairly large doses of nicotinic acid by mouth produced any effect upon the degree of porphyrin excretion.

Case 2 presents a picture of the usual course of porphyria. There was no family history to suggest porphyria in other members of this patient's family and no toxic agent could be shown to be a possible precipitating factor. Patients who have acute idiopathic porphyria and patients who have acute toxic porphyria present the same clinical picture and the same laboratory findings and probably represent the same disease, the only difference being that in one instance it happens to be possible to point out a substance which may have been a precipitating factor.

The description of Case 3 includes an interesting histologic study of tissues which were obtained at necropsy.

The fourth case represents the rather unusual condition of photosensitivity in the acute form of porphyria.

These 4 cases of acute porphyria were observed during the past 3 years. It would seem that the disease is not as unusual as has formerly been supposed and that with a more general knowledge of the subject more cases will be detected.

Summary and Conclusions. Acute idiopathic porphyria and acute toxic porphyria probably represent the same condition and both should simply be included under the term acute porphyria which is a disease caused by an inborn error of porphyrin metabolism.

The disease manifests itself clinically by any one or a combination of events which include a familial history; various types of gastro-intestinal disturbances and abdominal pain; red or dark reddish brown urine; involvement of the central nervous system, as evidenced by psychotic manifestations or paralysis, usually of the ascending type; jaundice; renal damage; and rarely pigmentation of the skin or dermal photosensitivity.

A discussion of the chemical aspects of the problem has been included and it is pointed out in what manner oxyhemoglobin and the zinc metal complex of uroporphyrin may be differentiated by spectroscopic means.

Case reports are presented of 4 patients who had acute porphyria and who have been encountered during the past 3 years and it is suggested that this disease entity is not so rare as hitherto has been supposed.

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PHOSPHORUS METABOLISM OF BLOOD OF PATIENTS WITH LEUKEMIA AND POLYCYTHEMIA.*

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In a previous paper[5] the distribution of radio-phosphorus (P^{32}) following its oral administration was noted in the blood of 2 patients with myeloid leukemia; and a suggestion was made that the rapid

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uptake of phosphorus by the white blood cells during the hours immediately following the administration was probably concerned with the carbohydrate metabolism of the cells, while that retained days after administration was probably associated with the nucleoprotein metabolism of the cells. This paper presents the amount of radio-phosphorus retained at various intervals of time in the "phospholipid," "acid-soluble," and "nucleoprotein" fractions of circulating red blood cells, white blood cells and plasma of patients with leukemia and polycythemia who received either orally or intravenously "therapeutic," and not "tracer," doses of radio-phosphorus.[3]

Materials and Methods. All of the patients had been diagnosed and treated elsewhere by means other than radio-phosphorus many months before admission. The radio-phosphorus was produced by the Berkeley cyclotron.[2] The separation[5] and fractionation[4] of tissues and cells have been described previously. The techniques might be summarized as follows: Cooled heparinized venous blood (the amount varying from 20 to 50 cc.) was centrifuged, the blood elements separated and each recentrifuged in heparinized buffer solution exactly 20 minutes at 1450 times gravity to insure constant volumes; and the "phospholipid" fractions were extracted by use of alcohol, ether and reflux condensers, the "acid-soluble" by ice cold 5% trichloracetic acid, while the residue was considered the "nucleoprotein" fraction. The radioactivity assays were determined by means of a DuBridge electrometer. The total phosphorus (P^{31}) content of the various fractions was determined by the method of Pregl.[5]

Results. The results are tabulated on the two accompanying tables. In Table 1 are listed the amounts of radio-phosphorus (P^{32}), as microcuries per cubic centimeter, or percentage of the dose administered per 100 cc. of packed red blood cells or packed white blood cells or plasma, retained in the various fractions 4 to 96 hours (21 days in one instance) after the administration of "therapeutic" doses of radio-phosphorus to 1 patient with lymphoid leukemia, 1 with myeloid leukemia and 2 with polycythemia. As can be observed, the greatest quantities of P^{32} were retained in the "acid-soluble" fraction of the red blood cells, white blood cells and plasma of all of the patients. However, the quantities in this fraction apparently reached a peak between the 12th and 24th hours after administration and then decreased, as did those of the "phospholipid" and "nucleoprotein" fractions of the red blood cells, but the quantities in the latter 2 fractions of the white blood cells and plasma gradually increased to the 96th hour, as can be observed. In 1 patient (Wer) equal amounts of radio-phosphorus were administered orally and intravenously and as is illustrated, much greater quantities were retained in all the fractions when P^{32} was given by the latter route.

In Table 2 are listed the average total phosphorus (P^{31}) content of the fractions of red blood cells, white blood cells and plasma of the 2 patients with leukemia. One finding of significance is that

TABLE 1.—RETENTION OF RADIO-PHOSPHORUS IN VARIOUS FRACTIONS OF THE CIRCULATING BLOOD OF PATIENTS WITH LEUKEMIA AND POLYCYTHEMIA.*

Name of patient and wt. in lbs.	Type of disease.	Amt. of P^{32} adm in μc.†	Route of adm.‡	Amt. of sodium phosphate in which P^{32} was incorp. (g.).	Hours after adm.	Red blood cells.						White blood cells.						Plasma.					
						Phospholipid.		Acid soluble.		Nucleo-protein.		Phospholipid.		Acid soluble.		Nucleo-protein.		Phospholipid.		Acid soluble.		Nucleo-protein.	
						μc/cc.†	% of dose/ 100 cc.	μc/cc.	% of dose/ 100 cc.	μc/cc.	% of dose/ 100 cc.	μc/cc	% of dose/ 100 cc.	μc/cc.	% of dose/ 100 cc.	μc/cc.	% of dose/ 100 cc.	μc/cc.	% of dose/ 100 cc.	μc/cc.	% of dose/ 100 cc.	μc/cc.	% of dose/ 100 cc.
Ab 135	Lymphoid leukemia	5000	O	.75	12	.0002	.0005	.0433	.0870	.0147	.0300	.0047	.0095	.0441	.0880	.0078	.0160	.0007	.0010	.0069	.0140	.0001	.0003
					24	.0006	.0011	.0593	.1180	.0162	.0320	.0096	.0192	.0413	.0820	.0107	.0210	.0013	.0027	.0053	.0110	.0001	.0003
					48	.0008	.0017	.0395	.0790	.0102	.0200	.0155	.0310	.0395	.0800	.0139	.0280	.0011	.0023	.0050	.0100	..	.0001
					96	.0007	.0013	.0235	.0470	.0086	.0170	.0178	.0356	.0373	.0745	.0227	.0430	.0007	.0010	.0037	.0070		
Kli 246	Myeloid leukemia	1950	I.V.	.30	4	.0011	.0066	.0114	.0630	.0123	.0620	.0029	.0150	.0320	.1700	.0044	.0230						
					24	.0014	.0075	.0121	.1140	.0085	.0440	.0064	.0330	.0312	.1680	.0095	.0490						
					48	.0006	.0043	.0078	.0460	.0054	.0280	.0061	.0310	.0263	.1500	.0121	.0630						
					96	.0011	.0066	.0057	.0330	.0029	.0150	.0093	.0480	.0192	.1080	.0172	.0890						
Wil 105	Polycythemia	6000	I.V.	.42	12	.0007	.0011	.0868	.1420	.0095	.0158	.0072	.0119	.0703	.1160	.0108	.0179	.0013	.0021	.0079	.0131	.0008	.0013
					24	.0008	.0013	.0660	.1090	.0510	.0850	.0156	.0258	.0763	.1260	.0163	.0271	.0031	.0051	.0051	.0083	.0020	.0033
					48	.0015	.0025	.0630	.1040	.0324	.0537	.0153	.0253	.0844	.1400	.0358	.0594	.0055	.0091	.0038	.0063	.0015	.0024
					96	.0032	.0053	.0336	.0557	.0226	.0376	.0063	.0104	.0457	.0748	.0315	.0523	.0070	.0116	.0032	.0053	.0029	.0048
Wer 184	Polycythemia	2550	O	.178	24	.0005	.0019	.0260	.1020	.0016	.0064	.0027	.0106	.0183	.0720	.0031	.0121	.0013	.0051	.0022	.0086	.0010	.0039
					48	.0008	.0031	.0230	.0900	.0086	.0338	.0051	.0200	.0236	.0925	.0171	.0668	.0022	.0086	.0039	.0153	.0017	.0066
					96	.0009	.0035	.0211	.0825	.0067	.0259	.0120	.0470	.0223	.0875	.0177	.0695	.0029	.0114	.0022	.0086	.0002	.0007
					21 da.	.0014	.0055	.0032	.0126	.0008	.0031	.0050	.0196	.0060	.0235	.0055	.0216	.0018	.0070	.0004	.0019	.0001	.0003
		2550	I.V.	.167	24	.0029	.0114	.0490	.1920	.0011	.0043	.0142	.0556	.0221	.0865	.0078	.0306	.0034	.0133	.0027	.0106	.0005	.0019
					48	.0034	.0133	.0338	.1320	.0088	.0345	.0271	.1070	.0700	.2750	.0226	.0885	.0110	.0431	.0022	.0086	.0005	.0019
					96	.0030	.0118	.0208	.0815	.0062	.0243	.0452	.1750	.0526	.2070	.0293	.1150	.0052	.0204	.0019	.0074	.0006	.0023

* All calculations corrected for weight of patients (to 150 pounds) and for decay of P^{32} to date of administration.
† μc. = microcuries. ‡ O = oral; I.V. = intravenous.

there is much more phosphorus in the nucleoprotein fraction of lymphoid than myeloid leukemic cells. This is probably due to the relatively greater volumes of the nuclei of these particular lymphoid cells.[1] Another finding is, that there is very little phosphorus present in the "nucleoprotein" fraction of plasma.

TABLE 2.—AVERAGE (FOUR DETERMINATIONS FOR EACH FIGURE REPRESENTED) TOTAL PHOSPHORUS (MG. OF P^{31} PER CC.) CONTENT OF THE FRACTIONS OF THE BLOOD OF 2 PATIENTS WITH LEUKEMIA.

	Ab (lymphoid leukemia).	Kli (myeloid leukemia).
Red blood cells:		
Phospholipid	.71	.11
Acid soluble	.51	.37
Nucleoprotein	.25	.11
White blood cells:		
Phospholipid	.52	.43
Acid soluble	.94	.56
Nucleoprotein	3.04	.89
Plasma:		
Phospholipid	.04	
Acid soluble	.08	
Nucleoprotein	.003	

There is no evidence that cells can distinguish radio-phosphorus (atomic weight of 32) from non-radioactive phosphorus (atomic weight of 31).

Discussion. At the beginning of the study it was hoped that a comparison of the findings between similar cells of the patients, particularly the white blood cells in the three types of disease, would be possible if corrections for body weight and dosage of P^{32} and P^{31} were made. The findings of one case (Wer) who had received the same quantity of P^{32} by different routes indicated that the factor of route administration would have to be considered also. However, before such comparisons could be possible, among other factors, the metabolic rate and the total volume of the circulating blood elements studied would have to be known. Therefore comparisons of findings between the patients reported here are impossible.

Summary. 1. Therapeutic doses of radio-phosphorus (P^{32}) were administered to 1 patient with lymphoid leukemia, 1 with myeloid leukemia and 2 with polycythemia.

2. The largest portions were retained in the "acid-soluble" fractions of red blood cells, white blood cells and plasma of patients with leukemia and polycythemia 4 to 96 hours after the administration. The peak of retention occurred 12 to 24 hours after administration.

3. In the red blood cells, the level of retention of P^{32} in the "nucleoprotein" fraction reached a peak before the 48th hour and then declined, while that of the "phospholipid" fraction increased constantly, at least until 21 days after administration. In the white blood cells, the levels of retention in both the "phospholipid" and

"nucleoprotein" fractions constantly increased during the period of 96 hours but not for 21 days. In the plasma, the "phospholipid" levels of retention increased and the "nucleoprotein" levels decreased during the same period in general.

4. The concentration of P^{32} in the various fractions reached higher levels following its intravenous than its oral administration.

5. Comparison between the findings in the three types of disease was not possible because of the undetermined effect of such factors as route of administration, metabolic rate and total blood volume.

6. These findings indicate that, of a quantity of phosphorus (P^{31}) ingested by humans, various amounts are absorbed and excreted by the circulating red blood cells, and that the peak of exchange occurs between 12 and 24 hours after consumption. A similar exchange takes place in the circulating white blood cells, which, however, retain phosphorus in the "phospholipid" and "nucleoprotein" fractions for much longer periods and in greater quantities than the surrounding red blood cells. The plasma also has a specific rate of phosphorus exchange. The characteristic trends of exchange of phosphorus in various fractions of the red blood cells, white blood cells and plasma are similar in the 4 patients in spite of the different disease processes involved.

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MAY THE DISEASE COMPLEX THAT INCLUDES MEGA-ESOPHAGUS (CARDIOSPASM), MEGACOLON AND MEGA-URETER BE CAUSED BY CHRONIC VITAMIN B_1 DEFICIENCY?

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Mega-esophagus (so-called cardiospasm) and megacolon are very common conditions in certain parts of Brazil and have been studied there from various angles for many years. The knowledge thus gained concerning them has enabled us to form concepts on the subject which are practically unknown elsewhere.

We have strong evidence that mega-esophagus, megacolon, pyloric achalasia (pylorospasm), mega-ureter, alterations in gastric chemistry and electrocardiogram with associated polyneuritis and low metabolic rate, are probably varied manifestations of a degener-

ative disease of the autonomic intramural nervous system caused by a chronic deficiency of vitamin B_1. A study of the diet of the patients revealed considerable evidence in favor of this concept of the disease.

Our personal clinical experience is based upon a study of 170 cases and our pathologic studies upon 16 autopsies. The studies of the geographic distribution of the disease is based on 626 cases, 549 of them on record at the Santa Casa de São Paulo during the last 18 years.

For purpose of clarity let us consider first the evidence in favor of a single fundamental pathogenesis, and, second, the evidence which points to a chronic B_1 deficiency as the etiologic factor.

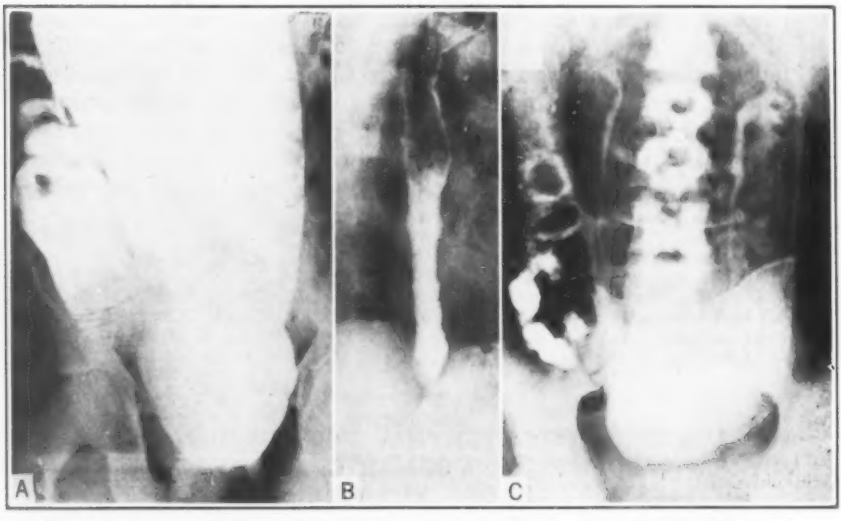

FIG. 1.—Case 1. Enormous megacolon, mega-esophagus of small dimensions and ureters with evident stasis.

Clinical evidence has progressively been accumulated in the literature tending to demonstrate that mega-esophagus and megacolon are related manifestations, possibly of common etiology, and permits expansion of this concept to include other associated morbid findings (Figs. 1, 2, 3).

Neiva and Penna[21] called attention to the association in the same individual of mega-esophagus and megacolon. Hurst[9,11] attributed to mega-esophagus and megacolon a common pathogenesis, namely, achalasia of the respective sphincter. Correia Neto[5a] found that mega-esophagus and megacolon are present concomitantly in 63% of 22 cases studied.

Pylorospasm, or more correctly, achalasia of the pylorus, has been described in association with mega-esophagus and with

megacolon in adults[34] and infants. Lehmann[16] considers pylorospasm as an equivalent of mega-esophagus and megacolon. Correia Neto[5c] observed 5 cases of achalasia of the pylorus in adults with concomitant mega-esophagus and megacolon.

FIG. 2.—Double mega-ureter in a patient with mega-esophagus and achalasia of the pylorus.

Hurst and Jones[10] included mega-ureter under the same pathogenesis of mega-esophagus and megacolon; this view was later adopted by Lehmann.[16,22] We observed[8c] this association in 3 out of 16 autopsies on patients with mega-esophagus. Mega-esophagus, achalasia of the pylorus, double mega-ureter with hydronephrosis and hypertrophy of the bladder were present together in one case (Fig. 2); in the second, there was mega-esophagus, megacolon, unilateral mega-ureter and hypertrophied bladder; in the third, there was megacolon with unilateral mega-ureter. The similarity

of the digestive and urinary tracts considered anatomically and functionally is very striking since both possess smooth muscle, several involuntary sphincters, and are innervated by a comparable intramural autonomic nervous system.

The presence of such sphincters in the digestive tract is unquestioned(Aloj[1]). Although there may be some argument concerning the exact location of alleged sphincters in some segments of the digestive and urinary tracts, there is no doubt of the existence of specialized function in these areas. The cardiac, pyloric, pelvirectal and internal anal sphincters in the digestive tract and the pyelo-uretheral, urethero-vesical and internal vesical in the urinary tract are all commonly accepted. Clinical and radiologic obser-

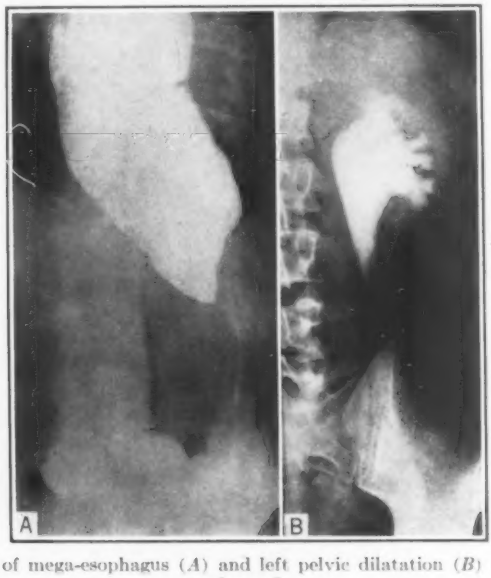

FIG. 3.—Case of mega-esophagus (*A*) and left pelvic dilatation (*B*) with excretory pyelography.

vation brings out the fact that dysfunction in any areas with sphincteric function produces dilatation proximally.

Hurst[9,10,11] suggest that the primary factor in the pathogenesis of mega-esophagus, megacolon and mega-ureter is achalasia of the sphincter, that is, absence of the sphincter relaxation which normally occurs on the arrival of the peristaltic wave. Simple absence of normal relaxation without any added spasm of the sphincter is sufficient to prevent the uninterrupted passage through the sphincter. This theory is now accepted as demonstrated by repeated confirmations.[2,4,6,8a,b,f,22,25]

This sphincteric dysfunction establishes a functional obstruction resulting in stasis above it. There follows, of course, a compensatory

change represented by increased peristalsis of the proximal segments going on to hypertrophy of the musculature. Thus the circular muscle of the esophagus, of the pylorus, and of the colon may become 3 to 4 times thicker than normal, the hypertrophy being required to overcome the sphincteric inertia. Notwithstanding this fact, the sphincter itself does not hypertrophy. This observation is based on the autopsied cases and is in accord with the theory of achalasia proposed. As these changes continue, a state of decompensation is reached when the hypertrophied musculature is no longer capable of overcoming the sphincter inertia. Then, the period of dilatation is initiated and with this, the symptoms usually make their appearance. The process culminates in atony and extreme degrees of dilatation.

The intramural autonomic nervous system extends throughout the entire digestive and urinary tracts. In the digestive tract it is formed by Meissner's plexus, in the submucosa and Auerbach's plexus in between the circular and longitudinal muscular coats. The latter plexus is made of nerves and ganglion cells of two types; multipolar cells (Type 1) and unipolar cells (Type 2 of Dogiel). The cells of Type 1 are motor in function and belong to the vagal and sacral autonomic system. The cells of Type 2—according to Dogiel's theory—should produce the peripheral reflexes of the intestinal wall.

The disposition of these cells in the alimentary tract is of great importance. The esophagus has cells of Type 1 only. In the stomach the cells of Type 2 are first seen near the pylorus. From there onward their number increases; in the jejunum they are abundant but the largest number is seen in the ileum, where the proportion compared with Type 1, is 50%. From the cecum onwards, the disposition is changed; again the multipolar cells (Type 1) begin to predominate and in the rectum, as in the esophagus, only cells of Type 1 occur. The esophagus and the rectum thus have a similar autonomic innervation.[12-15,18,20,26]

An interesting point demonstrated in our autopsied cases is the relation between the sphincters of the digestive tract and the cellular components of Auerbach's plexus. Directly above the sphincter there are many more cells than elsewhere in the alimentary tract.

The intramural autonomic nervous system of the ureter and bladder is made up of the same type of cells.[30]

I described the finer neuropathologic alterations of Auerbach's plexus in mega-esophagus in 1934.[8a,b,f] The methods used were those of Bielschowsky-Gross for the neurofibrillar apparatus and Nissl's for the study of the nerve cells. The alterations of the cells were dislocation of the nucleus to the periphery, central chromatolysis, micro-vacuolization and degeneration of the protoplasm. Bielschowsky-Gross's method showed pyknosis of the nucleus,

expulsion of the nucleus, destruction of the neurofibrillar system and neuronophagia. The alteration of the axis-cylinder can be classified as cleavage, retraction balls of Cajal, argentophilia and thickening and fragmentation of the axis-cylinder (Figs. 4 and 5).

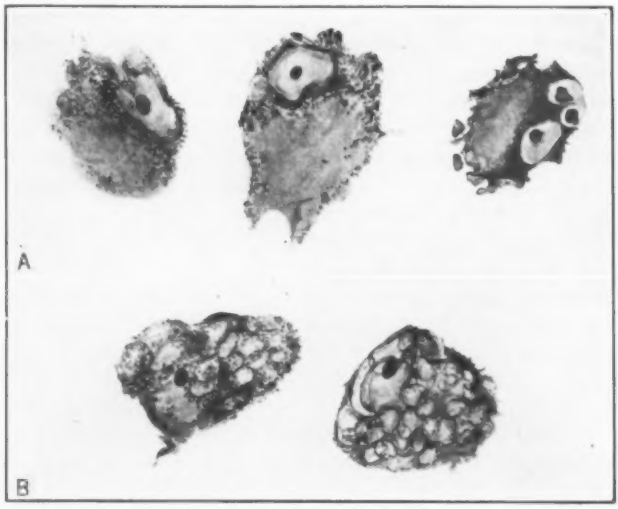

FIG. 4.—Mega-esophagus, lower third of the esophagus. *A*, Cells of the plexus of Auerbach with central chromatolysis; *B*, cells of the plexus of Auerbach with vacuolization and degeneration of the cytoplasm. (Nissl's stain.)

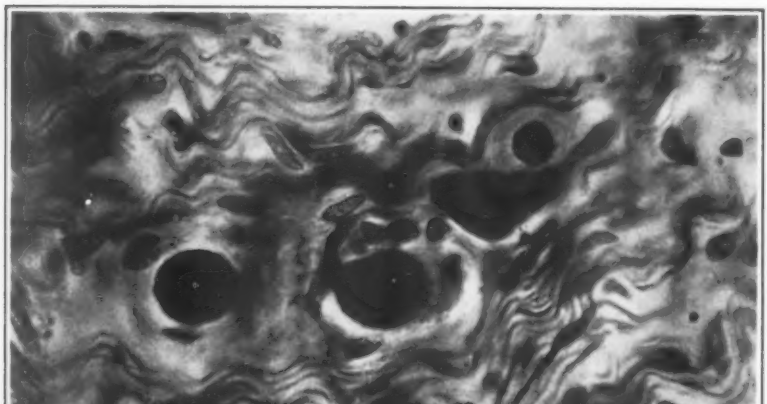

FIG. 5.—Mega-esophagus, lower third of the esophagus. Retraction balls and cleavage of axis cylinder. (Bielschowski-Gross's stain.)

Investigating a case of advanced bilateral mega-ureter, I was unable to even find the intramural nervous elements. These lesions

are typically degenerative. In order to demonstrate that they are not secondary to the mere dilatation with consequent rupture of these elements, the cardia of dogs was partially occluded by ligature. This resulted in dilatation of the esophagus, but even after 4 months the plexus was found to be quite normal.[8g]

We believe this degeneration is the result of a selective acting agent and thus is primary in type and not secondary to some factor influencing the entire involved organ.

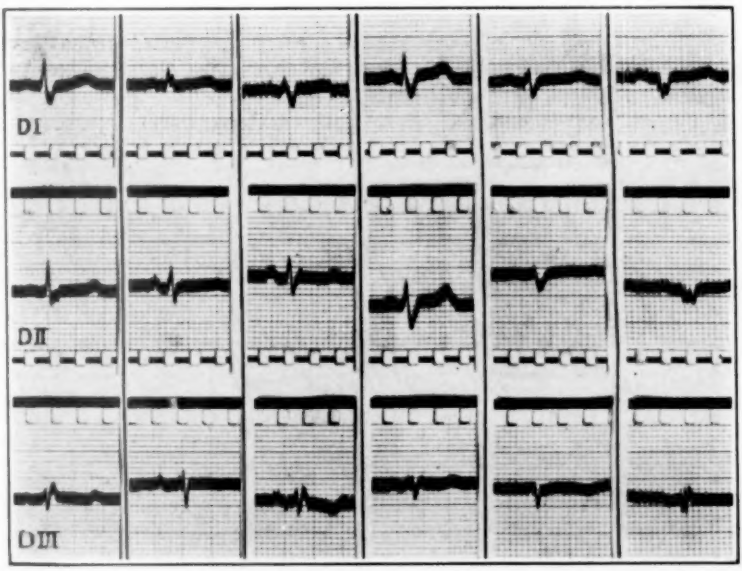

FIG. 6.—Electrocardiograms of 6 cases of: *A–B–C*, mega-esophagus; *D–E*, megacolon; *F*, mega-esophagus and megacolon.

Faced by these facts, it seems but a naturally logical step to visualize all of these manifestations as being produced by the same fundamental etiology, that is, the destruction of the intramural autonomic system. Further, the hearts of such patients also becomes injured. Neiva and Penna[21] called attention to the frequent complaint of palpitation in cases of mega-esophagus and megacolon. Sterling[27] and Villela[33] described electrocardiographic alterations in cases of mega-esophagus but failed to correlate these with other morbid findings.

Studying 24 unselected cases of mega-esophagus or megacolon or both conditions occurring concomitantly, we[8c,8d] found electrocardiographic alterations in 70.8% of the cases (Figs. 6 and 7). These patients were almost always younger than middle-age and did not complain of cardiac symptoms. A slow pulse rate was of

frequent occurrence.[8] Other investigations subsequently brought out confirmatory evidence of this primary report. Thus, Ramos[27] studied our 24 cases mentioned, added 7 other cases, and made clinical observations showing that these alterations of the electrocardiogram consist of disturbance of the conductive system; the electrocardiogram shows disturbances from the simple prolongation of the *QRS* complex to bundle-branch block. Ramos concluded that the destruction of the autonomic nervous system of the heart could explain the alterations of the electrocardiogram. Vasconcelos and Botelho[32] investigated the autonomic nervous system of the heart in cases of mega-esophagus having electrocardiographic changes and could not find even traces of this nervous system. Ramos and Oria,[24] in the hearts of my autopsied cases of mega-esophagus and megacolon, were able to demonstrate destructive

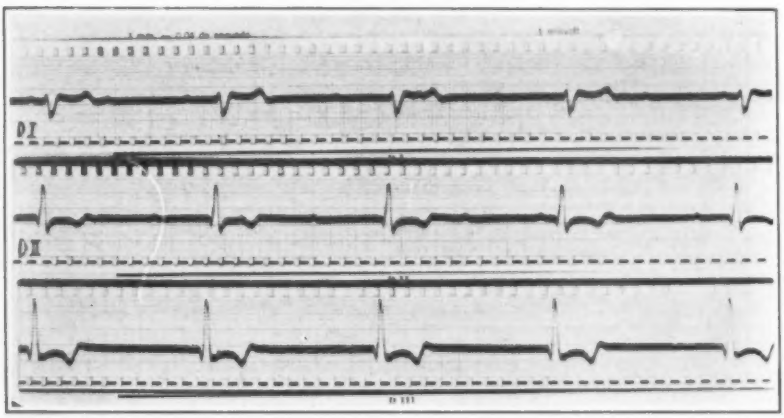

FIG. 7.—Case 1. Electrocardiogram showing partial *a-v* and bundle-branch block.

lesions in the autonomic intramural system in cases with typical electrocardiographic changes.

Since the autonomic nervous system of the heart can be regarded as at least the equivalent of the plexus of Auerbach in the digestive tract and intramural plexus of the urinary tract, these changes can be visualized easily as being of the same nature.

Vampre[31] described the absence of the patellar reflex in patients having mega-esophagus. The patellar and Achilles reflexes may be diminished or absent. In severe cases the disturbances in the reflexes are generalized. The interpretation of this disturbance is obscure. It is called polyneuritis because it has a certain resemblance to the symptoms of classical polyneuritis. However, it is only by routine examination that this disturbance of the reflex is found, since it is rarely a source of symptoms.

Gastric chemical studies were made in 15 cases[8c] (9 mega-esophagus, and 6 megacolon). We found hypochlorhydria in 9 cases and achlorhydria in 2 cases. The Katch-caffein test was used in the determination of free hydrochloric acid; the histamine test was used in the cases of achlorhydria.

Correia Neto[5b] in a series of 22 cases of mega-esophagus and megacolon pointed out the presence of low metabolic rate in 40.7%.

The morbid association of mega-esophagus and megacolon can hardly be regarded as accidental. The autonomic nerve supply to all of these organs is so similar that it seems likely that a common factor is responsible for the functional disorder of them all. This led me (February, 1935)[8c,d] to regard mega-esophagus and megacolon as a manifestation of a diseased condition of the autonomic nervous system, the complete or partial destruction of which would result in the appearance of some or all of these associated disorders. This theory suggests that we are not dealing with several independent affections but with one that has varied manifestations.

Analysis of Cases. Substantiating the previous discussion, Table 1 illustrates the frequency with which these varied manifestations occur. This group of 29 cases were studied systematically for the lesions listed. Although other manifestations of the disease were not routinely sought, mega-ureter was found in 5, achlorhydria in 2, hypochlorhydria in 1, low metabolic rate in 3, and achalasia of the pylorus in 2.

TABLE 1.—THE RELATIVE FREQUENCY OF THE MANIFESTATIONS OF THE DISEASE IN 29 CASES.

Manifestations of the disease.	No. of cases.	%	Morbid associations. Mega-esophagus.	%	Mega-colon.	%	Alterations, EKG.	%	Alterations peripheral reflexes.	%
Mega-esophagus	23	78	23	100.0	13	56.5	13	56.5	9	39.1
Megacolon	19	64	13	68.4	19	100.0	12	63.1	3	15.7
Alt. of EKG	18	62	13	72.2	12	66.6	18	100.0	6	33.3
Alt. of peripheral reflexes	9	31	9	100.0	3	33.3	6	66.6	9	100.0

The typical picture of these patients is exemplified in the 3 case reports.

CASE 1.—J. S., aged 22, negro, Brazilian farm laborer, 6 months before we saw him, began to have constipation with 2 or 3 days between evacuations. This disturbance became progressively worse and after 2 months the feces were expelled in hard fragments, the intervals between evacuations increasing. He had not had a stool in the previous 15 days. At the onset, he began to have difficulty in swallowing, as the food seemed to stop near the ensiform cartilage. In this same region pain occurred soon after eating. By taking water the food descended but at times the water was regurgitated, the food passing on to the stomach.

Physical examination showed the apex beat at the 4th intercostal space in the mammary line; a soft systolic murmur was heard throughout the

cardiac area. A tumor of great size was palpated in the central portion of the abdomen and in the left.

Radiologic examinations: Colon: mega-sigmoid (Fig. 1). Esophagus: mega-esophagus of small dimension. Heart: the cardia carea measured 130 cm.,[3] an approximate increase of about 30%. The radiologic aspect is of a general cardiac enlargement. Ureters: evident bilateral ureteral stasis (by excretory pyelography) (Fig. 1).

The electrocardiogram showed total A–V block; bundle-branch block (Fig. 7). The basal metabolism rate was −12%. The Wassermann blood test was negative.

This case presented megacolon, mega-esophagus, ureteral stasis and total A–V block with bundle-branch block.

Case 2.—J. M., aged 26, white, Brazilian, farm laborer, had had dysphagia for the past 4 years. At the onset there was a marked substernal burning sensation. Five months later dysphagia developed as a sensation of food stopping near the ensiform cartilage, which compelled him to take water during meals. It became worse until the patient needed to drink more and more water in order to force food into the stomach. A year ago he became much worse, drinking great quantities of water during meals, he experienced a sensation of the sudden passage of the food into his stomach. Five months ago he began to regurgitate food and water. There was constipation, the stools being hard and being passed approximately once in 3 days.

Physical examination revealed nothing of particular interest.

Radiologic examination: Esophagus: mega-esophagus; colon: extreme elongation and dilatation of the sigmoid and rectum.

The electrocardiogram showed slight right axis deviation and slurring of *QRS*.

This case presents mega-esophagus; megacolon with moderate symptoms of constipation. The electrocardiogram showed only small alterations.

Case 3.—L. B., aged 15, white, Brazilian, farm laborer, had constipation of 1 month's duration. Prior to this there had been daily bowel movements and no symptom of the digestive tract disturbance. At the time of patient's admission to the hospital there had been no bowel movement for 2 weeks. During the preceding 2 weeks as many as 5 days had passed without a bowel movement. Discomfort and vague abdominal pains were relieved by the passage of gas. Cathartics had little effect. The abdomen increased greatly in size and seemed to contain a hard tumor.

Examination of the heart showed apex beat at the 3d intercostal space in the left parasternal line; soft systolic murmur at the mitral area; accentuation of the aortic second sound; extrasystoles. A hard tumor more palpable in the central and left portions of the abdomen.

Radiologic examination showed an elongation and dilatation of the colon. The esophagus was normal. The cardiac area was normal.

The electrocardiogram showed arborization block. Auricular extrasystoles transmitted and blocked. Nodal ventricular escape. The basal metabolism was −66%. The Wassermann blood test was negative.

Case with megacolon, severe alterations in the electrocardiogram with negative cardiac clinical findings and low basal metabolism.

Considering the strong evidence in favor of a fundamental etiology for all of the varied manifestations correlated above, a statistical review of 626 cases was made[8a] in an effort to obtain a clue as to the nature of the etiologic agent. From the data collected, several very important points became manifest.

The ages of patients having any one of the above manifestations

of the disease ranged from 2 to 79 years (Chart 1). The greatest number, however, was between the ages of 15 and 25; the majority was admitted before the age of 40 (76.5%).

In 229 of the 626 cases, the age and onset of symptoms were obtained (Chart 2). In 58% of these 229 patients the symptoms began before the age of 25 years and the majority was between 15 and 25 years. Sex apparently had no influence in the age of the onset of symptoms; 89.2% of the patients were white, 79% were males. Farm-hand was the profession in 83% of the male components of this group.

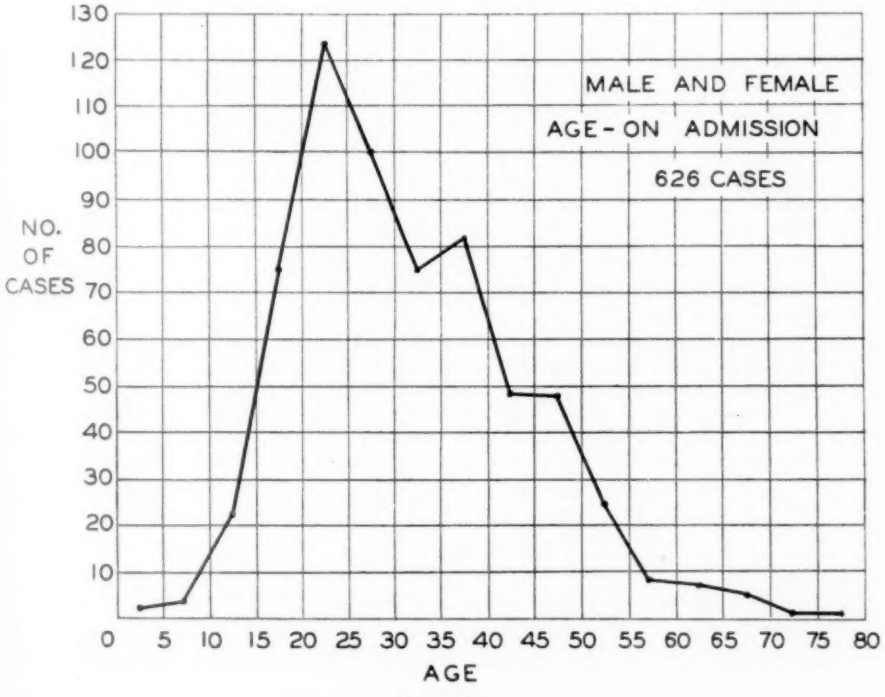

CHART 1.

Thus, the disease occurs by preference in young males from the rural sections.

A more detailed study of the geographic distribution brought out the fact that the majority of the patients come from the rather poor central and northeastern parts of the State of São Paulo. There were no cases from the coastal region. Further, those patients who happened to come from a richer zone in the state were found to have been born in sections of the state or migrated from portions of the country which were poor. There were 58

foreigners included in this group; of these 28 were Italians, 26 of whom came from near Venice where dietary deficiency manifested notably as pellagra is very common.

Thus, there is a strong suggestion that a dietary deficiency may be responsible for these manifestations.

The dietary[8b,c] habits of the people from the zones of the state where the disease is most frequently found are very well known and quite unvarying. The diet consists of beans, polished rice, flour of manioc and crude cane sugar. Occasionally dried meat, eggs, potatoes, vegetable and milk are added. Such a diet is deficient in vitamin B_1.

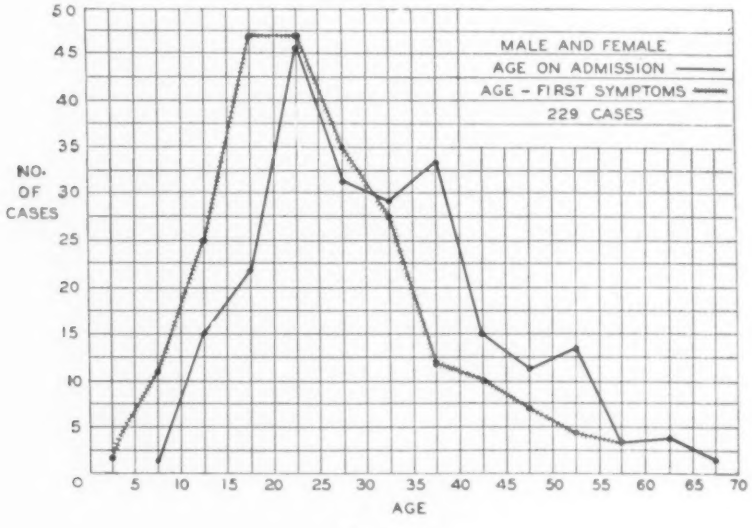

CHART 2.

Comparing beriberi and mega-esophagus with its related manifestations, we[8d] find that the manifestations of the two disorders are similar. Japanese[28] observers report lesions of the autonomic nervous system occurring in beriberi, as we have shown them to occur in mega-esophagus. Digestive disorders such as achlorhydria, vomiting and constipation, and cardiac and peripheral reflex disturbances are also common in beriberi.

The literature dealing with the pathology of vitamin B_1 deficiency indicates that it is frequent in poorly organized diets producing a latent or chronic state of insufficiency. Further correlation has been made between vitamin B_1 deficiency and various morbid conditions such as changes in the plexus of Auerbach (McCarrison[17a,b]), pylorospasm (Brodie[3]), obstipation (Montague,[19] Vorhaus, Williams and Waterman[36]). Further, it has been related to the total caloric intake more especially in predominantly carbohydrate diet which

requires a greater supply of the vitamin B_1 (Cowgill[7]). A lowered metabolic rate (Vorhaus[35]) and cardiovascular disturbances (Weiss and Wilkins[37]) have also been correlated with its deficiency. The human diet, even when very restricted, is always varied to a certain extent. By varying the diet, the sources of vitamins are also varied. Not having a constant deficiency of vitamin B_1, but a fluctuating deficiency, the morbid manifestations would be expected to vary accordingly in their degree of intensity.

Thus, we see that the disease occurs predominantly in young males of the laboring classes coming from regions where, for economic reasons, the diets are relatively unvaried and largely composed of carbohydrates and deficient in vitamin B_1. Being young male laborers, their total caloric demands are high. Their diet aside from being relatively deficient in vitamin B_1, is largely made up of carbohydrates and thereby increases the demand for vitamin B_1[7] (caloric-vitamin ratio of Cowgill). Those found in the more prosperous regions had moved there from the areas where the disease was endemic after a considerable period of latent deficiency.

The degeneration in the plexus of Auerbach is irreparable, and although some symptomatic improvement has been noted when treating these cases with vitamin B_1,[8,29] we cannot claim actual regression. Conversely, those patients who develop symptoms in the presence of an adequate diet indicate that although further degeneration may have been prevented by the adequate intake of vitamin B_1, the early changes of stasis or achalasia were present prior to migration, leading to hypertrophy and finally decompensation of the musculature, thus becoming symptomatic. Although no definite data have accumulated concerning vitamin therapy, its use seems justifiable.

Summary and Conclusions. The data presented tend to show that mega-esophagus (cardiospasm), megacolon, achalasia of the pylorus, mega-ureter and disturbances in the cardiac conduction system are but varied manifestations of the same disease. Achlorhydria, low metabolic rate and polyneuritis (peripheral reflex changes) are thought to be in the same clinical picture, even though not as clearly so.

Degeneration in the intramural autonomic nervous system is believed to be the anatomic basis for these manifestations.

A chronic or intermittent deficiency of vitamin B_1 is suggested as the etiologic agent responsible for the degeneration in the autonomic nervous system, thereby instituting a series of physiopathologic changes which culminate in the clinical picture described.

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SPONTANEOUS BERIBERI OF THE MONKEY AS COMPARED WITH EXPERIMENTAL AVITAMINOSIS.

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In 1940, many animals of the monkey colony (*Macacus sylvanus*) at the Pasteur Institute of Morocco showed evidence of a disease never previously observed in this 5-year-old colony. The disease, characterized clinically by an association of polyneuritis and cardiac weakening, and pathologically by cardiac and nervous lesions, was quite similar to human beriberi. A comparison of our sick animals with monkeys fed experimentally-deficient diets appeared convincing enough to explain the disease on the basis of a partial vitamin B_1 deficiency. Our results also provided a basis for general conclusions on the nature of beriberi.

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I. Clinical and Pathologic Findings. *Etiology.* The time of the appearance and the seriousness of the disease were dependent in part on the *age* of the animals. The adolescents, monkeys of about 3 years, were the first to be attacked (Nos. 1 to 6, Table 1). Younger animals, 1½ to 2 years old, exhibited the disease about 3 months after the first adolescent cases. All the adolescents and 7 out of the 20 young were attacked. In the affected young and in most adolescents the disease progressed to a fatal termination unless properly treated.

Of the 22 adults kept in the main room of the colony with the adolescents, only 1 was ill, with mild chronic symptoms (No. 30). In this room, ventilation, light, temperature and cleanliness were quite satisfactory. Two other adults kept in a smaller room, less well lighted and not regularly supervised, also showed chronic symptoms of the disease (Nos. 31 and 32).

Sex did not seem to influence the disease. The *species* might have played a rôle, since 2 Cercopitheci (*Æthiops sabæus*) in the same cage as the 2 sick adult macaques remained in perfect health.

Symptoms. After an insidious beginning the disease evolved irregularly, showing alternate periods of improvement and aggravation, generally ending in death within a few weeks to several months. The course of the disease could usually be divided into a prolonged phase characterized chiefly by neuromuscular disorders, followed by a terminal phase of acute dyspneic symptoms.

The earliest disorder noted was the animal's inability to leave the ground when preparing to jump. Climbing became clumsy, the gait unsteady, and the reduced activity caused the animals to remain seated in the cage most of the day (Fig. 1, *a*). As the disease progressed, the resting animal assumed a characteristic sitting posture with the lower limbs bent up in front and the head resting on the knees. It raised itself with difficulty, while standing appeared painful and became gradually impossible. The attempts to walk showed first a limping with a frequent unilateral predominance, that subsided while both sides became paralyzed and the animal could no longer keep its balance. A characteristic gait was observed in 2 cases, and suggested by many others: the animal moved the lower half of its body in one block, as if the lower limbs were fixed to the pelvis; when walking it would lean on the upper limbs to propel itself, using its arms as crutches. Muscular strength was much diminished, especially at the lower limbs. The animals had almost complete use of their upper limbs; some could even climb, hoisting themselves by their arms. In the 2 cases in which the evolution of the disease was experimentally accelerated (Nos. 9 and 10, Table 3), the paralysis extended to all four limbs. There was also a case of left facial paralysis (No. 6). When testing the muscular strength of the animals, it was noticed that they kept their lower limbs flexed, being unable to extend them. There

seemed therefore to exist some degree of muscular contracture. Muscular atrophy was marked. It predominated in the lower limbs and the pelvis. The muscles of the trunk (Fig. 1, *b*) and of the arm were involved too, although to a much less degree. However, in spite of the intense atrophy, electrical stimulation of the muscles showed no reaction of degeneration.

TABLE I.—SPONTANEOUS BERIBERI.

Animal No.	Sex.	Body weight		Approximate age, yrs.	Date of apparent beginning (1940).	Approximate duration, mos.	Hind leg paralysis.	Hind leg muscular atrophy.	Knee jerk.	Dyspnea.	Pulse.	Observations.
		Beginning, kg.	Death, kg.									
1	F	..	..	3	Mar.	2	+++	+++	.....	..	..	Dead, Apr. 23.
2	?	..	..	3	Mar.	2.5	+++	++	.....	..	..	Dead, May 15.
3	F	..	..	2–3	Apr.	3	+++	++	Absent	+	..	Dead, July 4.
4	M	..	2.06	2–3	Apr.	3	+++	+++	Absent	+	..	Sacr., July 10.
5	F	..	2.48	3	Apr.	3	+++	+++	Weak	+	165–110	Dead, July 22.
6	F	3.14	2.48	3	Apr.	6	+++	++	Weak	+	220	Sacr., Sept. 21.
7	F	3.48	..	3	July	3	++	±	Normal	+	228	Treat. B_1, Sept.
8	F	4.14	..	3.5	July	3	+	–	Normal	–	200	Treat. B_1, Sept.
9	M	3.60	..	3.5	July	..	±	–	Normal	–	280	See Table 2.
10	M	4.27	..	3.5	Aug.	..	+	–	Normal	–	..	See Table 2.
11	M	..	1.80	2	Aug.	1.5	+++	±	Weak	+	170	Dead, Sept. 7.
12	M	..	1.30	2	Aug.	1.5	+++	±	.....	+	..	Dead, Sept. 9.
13	M	1.51	..	1.5–2	Sept.	..	+	+	Absent	+	180	Treat. B_1, Sept.
14	M	2.08	..	1.5–2	Sept.	..	±	–	Weak	+	180	Treat. B_1, Sept.
15	F	1.91	1.20	1.5–2	Sept.	1	–	–	Weak	–	..	Treat. B_1, Sept.
16	M	1.85	1.75	1.5	Aug.–Sept.	1.5	++	±	Absent	+	..	Dead, Oct. 7.
17	F	1.38	..	1.5	Aug.–Sept.	..	++	±	Absent	+	180	Treat. B_1, Sept.
30	M	6.80	..	Adult	Mar.	7	++	+	Normal	–	220	Treat. wheat germ.
31	M	7.93	..	Adult	Apr.	6	++	++	Normal	+	190	Treat. B_1, Sept.
32	F	3.48	..	Adult	Apr.	6	++	++++	Weak	–	160	Treat. wheat germ.

Disturbances of the reflexes were variable. The knee jerk, normally pronounced in monkeys, sometimes appeared exaggerated at the beginning of the disease. In well-characterized cases, the reflex weakened gradually and finally disappeared. However, death would sometimes occur without complete abolition of the knee jerk (No. 6). The cutaneo-plantar reflex (Babinski sign) occurred in flexion as in normal animals.[5] Some degree of photophobia was found in 2 cases before death (Nos. 9 and 10). Disturbances of sensitivity were not well defined: there seemed to be some hypoesthesia of the lower limbs. Pain was apparently not present.

In the youngest monkeys the disease was revealed by acute attacks of *contractures* which usually lasted several minutes or (in 1 case) a few hours: the fingers were maintained flexed on the palms and the hands flexed on the forearms, with sometimes the aspect of wrist-drop. In only 1 case were there also painful cramps. Sometimes these attacks of contracture complicated a more or less

marked paralysis of the lower limbs (No. 13); sometimes they occurred in animals otherwise nearly normal (Nos. 14 and 15).

Cardiac disturbances manifested themselves at the beginning by a slight dyspnea when at rest and by more and more violent attacks of dyspnea occurring as a result of strain or emotional stress. The face was cyanotic. In younger animals, the increase in the number and amplitude of respiratory movements determined a deformity of the thoracic cavity which little by little produced a marked anterior prominence.

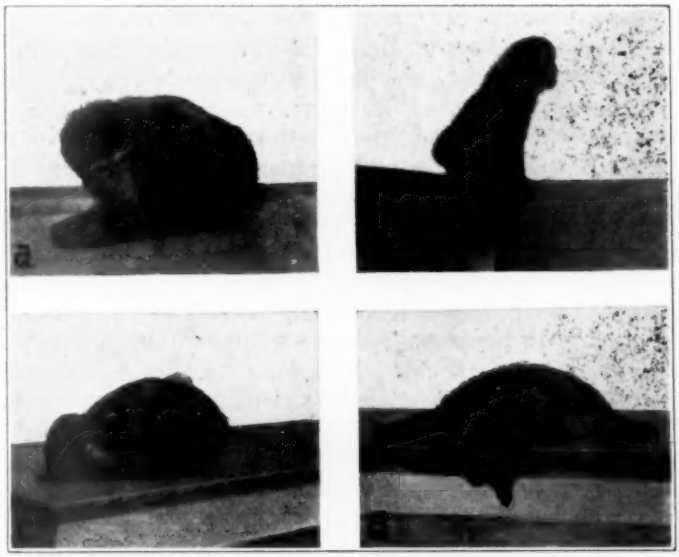

FIG. 1.—Above, two monkeys at the beginning of the disease, Nos. 4(*a*) and 5(*b*). Below, two monkeys at the terminal period, Nos. 6(*c*) and 9(*d*).

The pulse slowed down gradually as the disease progressed. Instead of 250 pulsations a minute as in the normal animal, one found a gradual diminution to 180 and even to 150 or less. Auscultation of the heart revealed sounds less defined than normally, with sometimes extrasystoles in the terminal phase. Cardiac symptoms predominated in 2 young animals (Nos. 16 and 17) in which the paralysis of the lower limbs was slight. The cardiac phenomena were much accentuated, especially the attacks of dyspnea that caused the death of 1 animal (No. 16).

The general condition of the animal became aggravated little by little. Besides muscular atrophy, there was emaciation of the whole body. The activity of the animal was restricted and the playfulness of the animals disappeared. The appetite decreased. No fever was observed.

The transition to the *terminal period* was progressive, but could be accelerated by emotional stress, such as occurred during clinical examination or any handling that determined marked reactions of the monkey. The animal was then no longer able to sit up or to walk, but lay with the head resting on the upper arms stretched in front of him (Fig. 1, *c* and *b*) or hunched in a ball with the head resting on the lower limbs. Besides a more flaccid paralysis the animals sometimes showed sudden shuddering or quivering localized in certain muscular groups (No. 11, Table 1; also 9 and 10, Table 3). By that time, cardiac disturbances increased. Attacks of dyspnea were more frequent and violent. The immobile animal ate very little or not at all; sometimes it had diarrhea and in 1 case, vomiting. Finally death occurred as a result of cardiac failure or cachexia. This end-phase lasted about 10 days.

Autopsy Findings. The nerves were examined in all but 3 cases by Marchi's and Weigert's methods (modifications of Nageotte and Spielmeyer). Characteristic Wallerian degeneration of the myelin sheath was found. While some fibers appeared normal or showed only foamy degeneration of the myelin, the disintegration was usually marked, extending frequently to the axone with a transformation of the myelin into irregular fatty droplets. The lesions predominated in the peripheral nerves, for instance the plantar nerve. In the main nerves, a comparison of the sciatic nerve as it emerged from the sacro-lumbar plexus with the ulnar nerve coming out of the brachial plexus showed a predominance of the lesions in the nerve of the lower limb. In monkey No. 6, with the facial paralysis, degeneration was found in the facial nerve on the stricken side. In every case examined, the vagus nerve was markedly attacked. On the whole, the lesions greatly exceeded those reported in classical descriptions of acute polyneuritis of the pigeon (Bertrand *et al.*).

There was no evidence of subcutaneous edema, but about 2 cc. of watery fluid was consistently present in the pericardial cavity. The heart was frequently hypertrophied. Three young animals dying of dyspnea presented an unusual deformity due to the expansion upward and forward of the anterior thoracic walls, causing the lower ribs to impress deep grooves on the upper part of the liver and the liver itself to herniate through the substernal attachment of the diaphragm in the form of small pediculated expansions about the size of a cherry. Frequently, pulmonary infarcts of various ages were found, probably as a consequence of right cardiac insufficiency.

The digestive tract showed signs of general atony, with abnormal distention of some segments of the small intestine and colon. Congestion was manifested by diffuse redness and ecchymotic points along the digestive tract; which occasionally appeared as well-formed ulcerations, especially in the pyloric region of the stomach. Mesenteric lymph nodes were greatly enlarged. Fatty degeneration

of the liver was frequent. The thymus glands were completely atrophied.

The genital activity slowed down. Histologic examination of the gonads showed no sperm formation in the adolescent males. All the females of the colony ceased menstruating and bearing young before the appearance of the first symptoms of paralysis.

Conclusions From Clinico-pathologic Observations. This incomplete and seemingly painless paralysis, with decrease of tendon reflexes save for the Babinski sign, suggested the existence of a polyneuritis. Since no symptom of intoxication or infection was found and the disease could not be transmitted by inoculations of blood or nervous tissue, the polyneuritis was ascribed to a dietary deficiency, namely beriberi. This diagnosis was confirmed by the heart disturbances, and the autopsy findings of hydropericardium and nerve degeneration.

II. Study of the Diet. Before September, 1939, the monkeys were in good health while given a diet of acorns supplemented with small amounts of stale bread, carrots, cabbages and sometimes sunflower seeds. When the war started, fresh acorns could not be obtained. The animals were given stale acorns which had been stored for a year and were spoiled to the extent that the substance of some of them was transformed into pulverized material. In February, 1940, the supply of acorns was exhausted. From that time on, the monkeys were given: 1, noodles or semoule (white barley meal), cooked alone or with chick peas and broad beans, these two latter given semi-weekly or less often; most of the monkeys ate little of or refused this paste as they dislike cooked food; 2, a small quantity of either carrots, or turnips or cabbage leaves, and 3, stale white bread *ad libitum*. Two months after this diet had been started, the first cases of beriberi appeared.

In Table 2, a tentative estimate of the amount of thiamin absorbed by the animals will be found. It could be only a rough estimation as the animals ate variable amounts of each item and there were variations in the diet according to the vegetables available. Finally, the figures for bread were possibly too high, for in Casablanca it was thoroughly bleached.

Table 2.

	Thiamin content (after Williams[11]) in gammas per gm.	Approximate amount eaten daily, gm.	Thiamin ingested daily, gamma.
Noodles	.5	5	2.5
Semoule	.1	5	.5
Chick peas	1.5	1	1.5
Broad beans	2.5	1	2.5
Carrot	.4	9	3.6
Turnip	.5	2	1.0
Cabbage	.2	7	1.4
White wheat bread	.5	20	10.0
Total	...	50	23.0

The requirement for thiamin was shown by Arnold in Elvehjem's laboratory[1,2] to be about 75 to 100 gamma of thiamin per 100 gm. of a low fat diet. This requirement was similar in all species studied, including man. In our monkeys' diet there were only 46 gamma of thiamin per 100 gm. of food.

From this dietetic history it may be concluded: 1, that the disease was not a toxic polyneuritis due to the damaged acorns, as the first symptoms were observed 2 months after the interruption of the acorn diet; and 2, that the diet was such as to produce a partial vitamin B_1 deficiency.

Comparison of the Observations With the Effects of Experimental B Deficiency. Because of the contrast between the numerous symptoms in human beriberi and the paucity of signs in the experimental B_1 deficiency observed in animals, there has been a general reluctance to hold the lack of thiamin as the only cause of beriberi.[9] Since the spontaneous beriberi of the monkey was polysymptomatic, as in humans, experiments were planned to determine whether an experimentally induced B_1 deficiency would also bring forth a similar nervous and cardiac syndrome. In a monkey given a diet of unwashed polished rice, as reported by Shiga and Kusama,[10] nervous and cardiac disturbances were strikingly similar to those of our cases of spontaneous beriberi.* On the contrary, in McCarrison's experiments, the monkeys died rapidly without outstanding symptoms.[6] In this case, the rice used for the diet had been completely deprived of thiamin by a sojourn of 36 hours in the autoclave.

TABLE 3.—EFFECT OF B-DEFICIENT DIET.

Animal No.	Sex.	Body weight.		Supplement.	Clinical symptoms at end of deficiency.				Cessation of diet.	Autopsy pericardial fluid, cc
		Before, kg.	Death, kg.		Nervous symptoms.	Diarrhea.	Asthenia.	Pulse.		
21	F	5.14	4.48	....	None	+++	+++	150	Dead, 33 d.	.5
9	M	3.60	2.90	....	Quadriplegia, no reflexes	+	+++	158	Dead, 8 d.	1.5
10	M	4.27	...	....	Quadriplegia, no reflexes	+	+++	180	Dead, 6 d.	2.5
24	F	1.99	1.82	....	None	—	+++	..	Dead, 40 d.	—
23	M	2.57	...	0.1 mg. B_1 semi-weekly	None	—	—	..	Interruption after 14 wks.	—
25	M	2.67	...	10 mg. B_1 semi-weekly	None	—	—	..	Interruption after 9 wks.	—

The diet given to our experimental monkeys was practically devoid of thiamin, since prolonged washing of the rice was shown by Spruyt[11] to reduce its thiamin content from 0.5 to 0.02 gamma per gram. The results (Table 3) indicated that, contrary to the controls maintained in good health (Nos. 23 and 25), the deficient adult (No. 21) and young (No. 24) died in 33 and 40 days respec-

* One case was also briefly reported by Schaumann.[8]

tively with very few symptoms. Histologic examination of the nerves (No. 21) showed only a minute foamy degeneration of the myelin. Therefore, as in McCarrison's cases, a *complete* thiamin deficiency had resulted in death before any prominent nervous or cardiac symptoms could appear, while the *partial* thiamin deficiency of the regular colony diet (and of Shiga and Kusama's case) had produced a chronic beriberi with multiple signs. Recently, several reports indicated that more numerous clinical or histologic symptoms were also observed in rat,[7] pigeon[13,14] and dog,[12] when the B_1 deficiency is not complete.

In the case of monkeys Nos. 9 and 10, they were the only adolescents of the colony that were not severely ill (Table 1) when they were given the experimental diet.* The effects of the diet were unusually rapid, since after 6 days (No. 9) or 3 days (No. 10), a sudden and complete flaccid quadriplegia set in, with muscular twitching and photophobia, resulting in death within 3 or 4 days. This rapid outburst of paralytic symptoms implied that these adolescents had no store of vitamin B_1, due to the fact that while on the colony diet they had used up more of the vitamin than younger (No. 24) and older (No. 21) animals. This confirmed the greater susceptibility of the adolescents to beriberi, as indicated in the section on the etiology of the disease. This acute outburst of beriberi strikingly recalls the "fulminating beriberi" observed in humans.[17]

In short, B_1 deficiency is either (*a*) *complete*, resulting in rapid death with few or no previous specific symptoms; (*b*) *partial*, resulting in beriberi; (*c*) partial at first, and suddenly complete, resulting in beriberi fulminans.

Therapeutic Assays. For the last 2 months (September and October, 1940) the monkeys of the colony, as well as 2 sick animals (Nos. 30 and 32) were given a handful of a thiamin-rich mixture of equal volumes of barley and wheat germ, in addition to their usual food. No new cases of beriberi have since appeared and the females began menstruating again.

Cure of sick monkeys with pure thiamin† (5000 to 50,000 gammas daily) failed in 3 animals at the terminal period. The lesions were probably too far advanced and the emotion due to subcutaneous

* The following diet was given *ad libitum:* Polished and washed rice, 87%; wet casein, 10%; salt mixture (McCollum's), 3%; in addition, they received semi-weekly, 5 cc. of cod-liver oil by pipette, and 35 mg. of ascorbic acid subcutaneously. Casein was prepared as follows: Milk powder was dissolved in 10 v. of water at about 80° C., precipitated with CH_3COOH at the same temperature and rapidly filtered on a vacuum funnel. Twice the precipitate was eluted in cold water at about 4°, in a slightly acidic medium, and filtered. Then it was gradually dissolved in a solution of CO_3NaH at 40°, which later was filtered Finally, a new precipitation was performed, the precipitate being again washed twice and most of the water being extracted by pressure. This diet was also partly deficient in B-complex factor, which fact was erroneously expected to facilitate the development of beriberi.

† Bevitine Rhone-Poulenc.

injections started acute attacks of dyspnea, sometimes producing the death of animals. Better results were obtained in 6 animals (Nos. 7, 8, 13, 14, 17, 30) treated by dissolving 5000 gammas of thiamin in drinking water daily.* The attacks of contracture completely disappeared in Nos. 13 and 14, the former appearing quite normal. The adolescent female (No. 8) began menstruating. Paralysis regressed in Nos. 7, 8 and 31, but it was not modified in No. 14. The animals, however, did not gain over or equal the weight previously lost. In short, a definite improvement was produced by thiamin, and at any rate, there was no aggravation, since probably most of these animals would have been dead by this time (November 1) had thiamin not been given. But the improvement was slow and did not seem to be complete.

The immediate cure of spastic phenomena was to be expected, as thiamin quickly suppressed opisthotonos and other spastic accidents in pigeons and other animals.[12–14] The very slow rate of improvement of the paralysis was due to the intensity of nerve degeneration, since the length of treatment for paralysis in B_1 deficiency was found to be proportional to the number of degenerated axones in the pigeon sciatic nerve.[13,14] Cowgill[3] and Street *et al.*[12] had even observed cases of well-advanced paralyses which could not be cured at all. As for the inability of the animals to regain their previous weight when treated with thiamin, this suggested the possibility of another food deficiency affecting the growth, possibly a lack of riboflavin, although carrots and cabbage contain a fair amount of it, or, as suggested by Cowgill† a lack of B_6, which might also account for some of the cardiac symptoms, as in cases described by Thomas *et al.*[15]

Discussion. It is well known that, in lower animals, a B_1-free diet produced few or none of the clinical symptoms and nerve lesions characteristic of beriberi.[4] In humans likewise, Williams *et al.*[18] did not observe marked clinical symptoms on a diet very low in thiamin. These findings were in agreement with the absence of clinical and pathologic disturbances in our experimental monkeys given a diet without thiamin.

On the other hand, a diet *partially* deficient in B_1, when given to lower animals, caused numerous clinical symptoms[13,14] and a marked nerve degeneration,[12] both suggestive of beriberi. In our cases of typical beriberi in the monkey, the thiamin content of the diet was estimated to be about one-half the minimal requirement.

On the basis of these observations, it seems reasonable to conclude that only when the deficiency of B_1 is partial does one obtain the clinical and pathologic picture considered as characteristic of beriberi.

* Five grams of glucose were added as suggested by Tonutti and Walraff.[16] The increased thiamin requirement due to this amount of glucose was negligible in view of the quantity of thiamin given daily.

† Private communication.

Conclusions. 1. Twenty cases of a cardionervous disease observed in a *Macacus sylvanus* colony have been described. Clinical signs of polyneuritis and cardiac failure, autopsy findings of peripheral nerve degeneration and hydropericardium, and a diet partially deficient in vitamin B_1, indicate beriberi as the cause of this disease.

2. The adolescent (3-year-old) monkeys were the most susceptible to the deficiency, as all were stricken early. In younger animals the disease occurred later, was characterized by spastic phenomena and intense cardiac disturbances leading to an early death. Some older animals showed chronic and moderate symptoms which did not result in death.

3. Treatment of the animals with crystalline thiamin cured the animals, but only incompletely, thus suggesting that a prolonged deficiency determines permanent lesions. Menstruation was resumed after treatment with either wheat germ or, in 1 case, pure thiamin.

4. In experimental complete B_1 deficiency, death occurred before any outstanding clinical symptoms or marked histologic degeneration of the nerves set in. However, when 2 sub-beriberic adolescents were given the B_1-free diet, acute symptoms reminding one of fulminating beriberi were observed.

5. The observations, including the failure of a complete lack of thiamin to produce the symptoms or pathology of beriberi, suggest that only a partial thiamin deficiency results in beriberi.

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VITAMIN B_1 NOT HELPFUL IN PROTRACTED INSULIN SHOCK.

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Protracted insulin shock sometimes follows a regular session of insulin shock treatment for schizophrenia. Usually the patient is awake within 15 minutes after sugar solution is given by nasal tube. But, exceptionally, even with the aid of intravenous glucose, the patient is not awake in an hour, and it becomes evident that he is in a state of protracted shock. Regardless of the amount of sugar given, he will not awaken for several hours or days or not at all. Or he may gradually respond aphasically, being none the worse for the experience, or may show adverse neurologic signs for months afterward.

In almost every article or discussion on the alleviation of prolonged coma, the injection of thiamin chloride has been advocated. However, Frostig[6] places no confidence in this remedial agent and recently Cleckley and Templeton[2] reported its inefficacy.

The routine of insulin shock treatment requires large amounts of carbohydrate, usually in the form of sugar solution, to awaken the patient. Abundant carbohydrate increases the thiamin requirement[15] and a high carbohydrate diet is most effective in producing the symptoms of B_1 avitaminosis. In the avitaminotic animal, minced brain tissue has not so great a capacity to utilize oxygen as in the normal animal.[16] On the addition of crystalline thiamin chloride to the test tube, avitaminotic brain tissue takes up increased oxygen, whereas the normal pigeon brain does not. Certain brain cells of the B_1-deficient pigeon have a lowered respiratory rate in the presence of dextrose, a condition remedied by the addition of thiamin chloride.[13] The latter increases oxygen consumption only in the B_1-deficient man or animal, relatively enormous doses being without effect in normals.[11] According to Holmes,[7] the taking up of oxygen by the gray matter is increased after the addition of dextrose and reduced during insulin. Damashek and Myerson[3] demonstrated in insulin shock a decrease in the use of oxygen in the brain and attributed the neurologic symptoms in hypoglycemia to this diminished oxygen content.

Chemical analysis of the minced brain of the avitaminotic pigeon reveals pyruvic acid and methyl glyoxal, both of which are absent in the normal. These abnormal metabolites disappear on the addition of thiamin chloride. After carbohydrate metabolism has been

disrupted by monoiodoacetic acid or hyperinsulinization, methylgloxal and pyruvic acid can be demonstrated in muscle. The theory has crystallized[12] that vitamin B_1 functions as a coenzyme in the metabolism of carbohydrate, more specifically in the oxidative breakdown of pyruvic acid. The great similarity of convulsions induced by thiamin deficiency, methylglyoxal and insulin has been pointed out.

There are other parallels between hyperinsulinism and B_1 avitaminosis. It is said that idioacetic acid or insulin overdosage leads to elaboration of methylglyoxal or pyruvic acid in toxic concentration, and that the mustering of sufficient vitamin B_1 reserve will overcome the toxicity from insulin. Dioxyacetone decreases insulin convulsions; pyruvic acid and methylglyoxal increase them.[4]

Demole[4] gave insulin shock to 39 rabbits with 1 unit of insulin per kilogram of body weight. Of these, 13 each got 4 injections subcutaneously of 500 units of thiamin chloride 2 hours preceding the insulin, while 16 rabbits got no vitamin B_1. Of the latter, 11 had convulsions, recuperating spontaneously; all comas lasted more than 7 hours, in all the blood sugar went below 50 mg. In the vitaminized rabbits, only 2 had convulsions, 1 recuperating spontaneously; all remained in coma less than 7 hours; 5 stayed above 50 mg. blood sugar and 8 under.

Freudenberg[5a,b] has often been quoted as the authority for the use of thiamin chloride to relieve protracted insulin coma. He had some insulin shock patients who, 30 minutes after being tube-fed with 400 cc. of 50% glucose solution, were not awake and who for several consecutive days had to be aroused with 140 cc. of 33% fructose intravenously. When given 2.5 gm. thiamin chloride 20 to 30 minutes after the tube feeding, the same patients awoke quickly, so that intravenous sucrose was not necessary. Freudenberg averred that administration of vitamin B_1 would improve the hypoglycemia even before sugar was given.

Leitao[10] induced shock in a patient with 50 units of insulin, reducing the blood sugar below 30. Three minutes after an ampoule of betaxin was given intravenously, the blood sugar was 39. Another patient was given shock with 60 units of insulin, the blood sugar many times being lower than 30. After 4 hours, shock was interrupted by intravenous injection of 3 ampoules of vitamin B_1. Two minutes after the injection, the blood sugar was 45 and 3 minutes later 53. The author was not explicit as to the intensity of the shock.

According to Akos,[1] vitamin B_1 prevents hyperactivity and convulsions during shock and protracted coma if the vitamin is injected 16 hours before the insulin. "The organism must have been previously saturated with the betaxin to be effective." In 2 of our patients, there did seem to be a lessening of hyperactivity when we gave 5 to 10 mg. of thiamin chloride intramuscularly 16 hours before the insulin daily, and no convulsions or prolonged comas occurred

TABLE 1.—EFFECT OF VITAMIN B_1 ON TIME OF AROUSAL FROM INSULIN SHOCK AFTER SUGAR-FEEDING IN 27 PSYCHOTIC PATIENTS.

Mode of administration.	Name of vitamin preparation.	Amount given.	Units of vitamin B_1.	No. of patients in group.	No. of observations.	Insulin dose in units.		No. of minutes of hypoglycemia before carbohydrate administration (plus vitamin B_1 where later given).		No. of minutes to awaken.	
						Range.	Mean.	Range.	Mean.	Range.	Mean.
By mouth (in tube-feeding)	Galen B syrup	½ oz.	1,500	17	90	30–330	172	180–334	255	0–57	20
By mouth (in tube-feeding)	Galen B tablet	½ tablet	1,500	7	38	55–190	144	165–307	262	4–40	11
		All cases given	1,500	17	128	30–330	164	180–334	259	0–57	13
	Galen B syrup	1 oz.	3,000	14	69	30–280	132	241–350	302	0–35	13
	Galen B tablet	1 tablet	3,000	12	69	30–300	124	242–344	294	−1–42	12
		All cases given	3,000*	14	138	30–300	128	241–350	298	−1–42	12
Subcutaneously	Thiamin chloride	1 cc.	3,000	13	73	25–240	122	221–345	288	−1–30	10.4
Intravenously	Thiamin chloride	1 cc.	3,000	14	50	40–320	122	224–345	289	−1–43	12
	All cases given		3,000†	14	123	25–320	122	221–345	288	−1–43	11
		All cases given	3,000	15	261	25–320	125	231–350	293	−1–43	12
Intravenously	Thiamin chloride	1 cc.	15,000	6	32	35–240	120	214–307	256	5–25	11
		All cases given vitamin B_1		27	421	25–330	127	180–350	280	−1–57	12
		Controls	...	27	229	25–340	147	168–349	271	−2–185	13

* Orally. † Parenterally.

Age Distribution: Range, 15–48 years; Mean, 29 years. *Sex:* 9 Males, 18 Females. *Period of Study:* October, 1938, to November, 1939.

in these 2 patients. In 1 of our cases, where 120 to 240 units of insulin was the shock dose, 100 mg. thiamin chloride daily may have decreased the hyperactivity during coma, but it did not eliminate it; in fact, we were forced to give the patient 3.5 gr. of sodium amytal during this stage, in addition to having an orderly with the patient to keep him from injuring himself by thrashing about. Cleckley and Templeton[2] reported prolonged coma in 1 patient who had previously been prepared with thiamin chloride.

Experiment. From October, 1938, through November, 1939, we tested the effect of vitamin B_1* on the arousal time of 27 insulin shock patients. During alternate periods, different patients were given no vitamin, so that at all times there was an equal number of controls and experimental subjects. The vitamin was tried by mouth, intravenously and intramuscularly, always just as we were ready to terminate the hypoglycemia by pouring the tube feeding, the tube being already in place. Our time of termination was 4 to $4\frac{1}{2}$ hours after the insulin was administered, the patient having been unconscious in each case about 2 hours. From the accompanying table, it is evident that this use of vitamin B_1 made no statistically significant difference in the arousal time of insulin shock patients.

Comment. Of course there is a dearth of experimental evidence with regard to prolonged insulin coma, since each investigator fortunately has experienced only a few instances. Such shock situations come mostly after many shocks which were promptly reversible. There is more danger of protracted coma in the period of increasing sensitivity to insulin, in the first week or two, particularly if the dosage is increased by leaps and bounds or when hypoglycemia is permitted to run longer than 4 or $4\frac{1}{2}$ hours. We know that in animals the long-protracted comas are not reversible.

Storage of thiamin is widespread in the body, the highest concentrations being in liver, kidney, heart and brain.[17] The latter retains most of its thiamin in B_1 avitaminosis even at the expense of other tissues. Animals deprived of vitamin B show disturbances of carbohydrate metabolism similar to those of diabetes, that is, the tolerance for dextrose is diminished.[9] "Severe degrees of diabetes are not observed but the level of blood sugar is elevated enough to provoke glycosuria when carbohydrate is administered to animals or men *long* deprived of vitamin B_1."[14]

In protracted insulin coma there is often hyperglycemia and fever, and it is useless in these cases to keep plying the patient with sugar when the brain cells are probably "in a histiotoxic condition, unable to utilize the sugar."[8] Heavy decrease of blood chlorides may also lengthen the shock.[8] "The great loss of chlorides through profuse sweating and increased production of gastric juice may explain these findings." In addition to salt feeding, Kant suggests pushing fluids in prolonged coma, as there is probably a disturbed water balance too.

* We are indebted to the Galen Company, Inc., Berkeley, Calif., for all of the vitamins used in our experiment.

We have given a full course of insulin comas to 80 patients, among whom there have been 4 prolonged comas. When the latter complication occurred, we continued treatment on small dosage of insulin after a rest period of a week, except that in one of our earliest cases we were afraid to take further chances. We have had no bad residua and no deaths. For termination of coma, it is our custom to tube-feed brown sugar dissolved in hot water. We weigh out 1 gm. of sugar for each unit of insulin. This has been sufficient, except in 1 case in which 1.5 gm. of sugar to each unit of insulin was required for prompt awakening. When less than 100 gm. of sugar is needed, we make the solution up to 500 cc.; when 100 to 150 gm. of sugar is used, we go up to 750 cc., and with 200 gm. of sugar or more, we give a liter of water. The sugar will absorb more quickly if boiled to a syrup, but this makes unnecessary work. For the last 8 months, we have added 4.5 gm. of sodium chloride to each tube-feeding, and have had no prolonged comas during this period.

Conclusion. According to the tests we have made with thiamin chloride during insulin shock, we would not expect it to be helpful in arousing a patient in protracted coma.

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STUDIES OF THE B VITAMINS IN THE HUMAN SUBJECT.

III. THE RESPONSE OF CHEILOSIS TO VITAMIN THERAPY.

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THE dependence of cheilosis on some nutritional disturbance was first suspected in 1911 when Stannus[9] observed the development of the lesion in native Nyasaland prisoners who subsequently presented

a pellagraderm. Then, in 1915, Bahr,[2] described the lesion among indigenous prisoners in Ceylon, more especially those serving long sentences. He stated that the prison warden ascribed the sores at the angles of the mouth to the eating of salt fish and regarded, as a valuable remedy, the ingestion of half-cooked liver or liver soup. It was not until 1937, however, that Aykroyd and Krishman[1] noted that cheilosis in their experience coincided with a deficiency of some factor or factors of the vitamin B-complex. In view of the development of the lesion on a riboflavin deficient diet, Sebrell and Butler[6] ascribed the lesion to a deficiency of that vitamin. Their observations were given support subsequently by the reports of Sydenstricker[10] Oden,[5] Spies[8] and Jolliffe,[3] who noted also a disappearance of the lesion following the administration of riboflavin.

The possibility, however, of a deficiency of other fractions of the B-complex being responsible, in part at least, for the development of cheilosis has been suggested by some of the reported data. Sydenstricker,[10] for instance, noted a subsidence of the affection in a pellagrin while he was receiving only nicotinic acid. The seemingly beneficial effects of the nicotinic acid in this case, however, were ascribed to an adequate riboflavin content of the diet, especially since the lesion appeared in another of his pellagrins while he was being treated with nicotinic acid. Manson-Bahr[4] also referred to some pellagrins in whom the cheilosis disappeared following the administration of nicotinic acid. Smith and Martin,[7] furthermore, saw the lesion clear up in a patient on a diet deficient in riboflavin. They also observed its disappearance in 3 out of 4 patients when pyridoxine was administered; and in a fifth case, that did not respond to riboflavin or nicotinic acid, they observed complete healing only when liver extract was administered.

This paper summarizes a personal experience in the management of 17 cases of cheilosis. It includes some negative results after the administration of riboflavin alone and some favorable responses to pyridoxine and nicotinic acid; it also suggests, in some instances, the importance of an adequate ascorbic acid blood concentration.

Description of Cases and Method of Study. During the past year 17 patients with cheilosis have been observed at the Philadelphia General or the University of Pennsylvania Hospital. All of them had been on an inadequate diet, and 15 presented, in addition to the typical lesion on the lips, other manifestations of B-complex deficiency, including chiefly glossitis alone or glossitis associated with bilateral calf muscle tenderness; 16 had anorexia; 3 had clinical and laboratory evidence of scurvy.

In 12 of the 17 cases the cheilosis was confined to the angles of the mouth and in one of these the lesion was unilateral. In 4 others it involved, in addition, the vermilion of the lip; and in 3 of these, that had scurvy, each lip was completely affected, and in the other one (S.B., Table 1) the involvement was confined to a wide shallow

ulcer on the right half of the lower lip. A similar ulcer, without involvement of the angles of the mouth, was present on the lower lip of the final case, a pellagrin. Bleeding occurred only in those patients who had scurvy.

TABLE 1.—CASES THAT RESPONDED FAVORABLY TO PYRIDOXINE (B_6) THERAPY.

Case.	Age.	Sex and race.	False teeth.	Location of lesion on lips.	Duration of lesion prior to treatment (mos.).	Other manifestations of deficiency.	Amount of pyridoxine received (mg.).	Time in which healing occurred (days).	Primary diagnosis.
E.L.*	60	F. W.	+	Both angles	?	Glossitis, calf muscle tenderness	70 in 7 days (H)*	7	Acute cholecystitis
B.C.†	24	F. W.	0	Both angles	1	Glossitis	210 in 7 days	5	Alcoholism
F.R.	33	F. W.	+	Both angles	> 2	Glossitis, calf muscle tenderness	270 in 9 days (H)	7	Anorexia nervosa
I.H.	25	F. W.	+	Both angles	12	Reddening of oral mucous membranes	375 in 5 days	3	Diabetes mellitus
J.C.‡	52	M. W.	Uncompensated edentia	Both angles	1	0	375 in 5 days	5	Tabes dorsalis
M.R.	61	F. W.	+	Both angles	24	0	525 in 7 days	3	Diabetes mellitus
G.H.§	73	F. W.	+	Both angles	2+	Glossitis	600 in 20 days	Incomplete in 26 days	Osteoarthritis
T.D.	32	M. W.	0	Left angle	2	Glossitis	1050 in 7 days	7	Malnutrition
S.B.	63	F. W.	+	Both angles with ulcer on lower lip	½ ?	Glossitis, peripheral neuritis	2100 in 14 days	14	Scleroderma, polyarteritis

* No response to previous course of nicotinic acid (3500 mg. over period of 9 days).

† Lesion recurred within 1 week after discontinuing administration of pyridoxine; permanent regression following second course of treatment and resumption of well-balanced diet.

‡ No response to previous course of riboflavin (92 mg. in 7 days).

§ Definite healing occurred during first 2 weeks of treatment, after which a course of riboflavin (75 mg. in 6 days) was substituted. The lesions became worse during period of riboflavin therapy but began to regress when pyridoxine was readministered.

H = subcutaneous administration.

The cases may be divided into two groups: one, including 5 outpatients, kept on their usual diet, and the other, including 12 in-patients, in whom some change in the dietary habits occurred incident to their hospitalization. In the latter group, however, though an adequate diet was presented to each subject, he was allowed to choose what foods he wished. All supplementary vitamins except the one that was being tested in the case at the time

were withheld. That vitamin preparation, except when noted otherwise, was administered by mouth. Local applications to the lips were not permitted.

Results. A trial of pyridoxine (B_6) was made in 13 of the 17 cases. The cheilosis in 9 (Table 1) of these healed while they were receiving this vitamin. The lesion in 8 of them subsided within 3 to 14 days. In the ninth case (G.H.), in which the cheilosis was

TABLE 2.—CASES WHICH RESPONDED TO VITAMIN PREPARATIONS OTHER THAN PYRIDOXINE.

Case.	Age.	Sex and race.	False teeth.	Location of lesion on lips.	Duration of lesion prior to treatment (mos.).	Other manifestations of deficiency.	No response* (mg. in days).		Response* (mg. in days).	Primary diagnosis.
A.K.	19	F. W.	0	Both angles	3 (?)	Glossitis	195 in 7 B_2	609 in 7 B_6	N.A. 630 in 7	Rheumatoid arthritis
G.C.	50	M. W.	0	Lower lip (shallow ulcer)	½	Glossitis, dermatitis, diarrhea, calf muscle tenderness			N.A. 7800 in 7	Alcoholism, pellagra
M.J.	44	F. C.	0	Both angles and limbs	1	Glossitis, low blood ascorbic acid level	N.A. 7200 in 12	B_2 21 in 7	Ascorbic acid 1700 in 13	Sicklemia, lues (treated), scurvy
M.G.	55	F. W.	+	Both angles and limbs	2	Glossitis, low blood ascorbic acid level	B_6 1800 in 12	B_2 180 in 6	Ascorbic acid 1200 in 4	Unilateral sciatica, scurvy
E.S.	32	F. W.	0	Both angles and limbs	½	Low blood ascorbic acid level	. . .	. . .	Ascorbic acid 2600 in 10	Scurvy
J.M.	44	M. W.	+	Both angles	2	Glossitis	B_6 420 in 14	B_2 49 in 7	Brewer's yeast 7.5 gm. t.i.d. in 14 days	Multiple sclerosis
F.M.	69	F. W.	+	Both angles	?	Glossitis	B_2 70 in 7	B_6 70 in 7	. . .	Multiple sclerosis (?)
M.K.	69	M. W.	+	Both angles	12	Glossitis, calf muscle tenderness	B_6 1050 in 7	B_2 64 in 14	Brewer's yeast 7.5 gm. t.i.d. in 14 days	Diabetes mellitus

* Nicotinic acid (N.A.); riboflavin (B_2); pyridoxine (B_6).

most severe, extensive and ulcerative, healing occurred only after 26 days; during this period riboflavin was substituted for the pyridoxine for 6 days, but during this time the ulcerations became worse, to regress on resumption of the pyridoxine therapy. The cheilosis in the other four patients (M.G., J.M., M.K., and F.M.; Table 2) treated with pyridoxine failed to improve during its administration. One of these (M.G.) received the vitamin subcutaneously

as well as orally. All of these also failed to respond to riboflavin. The course of their lesions will be described in another paragraph.

In 8 of the cases, including some that also received and responded favorably to pyridoxine, riboflavin therapy failed to produce any evidence of significant regression. Of these cases the lesion in 2 (J.C. and G.H.) responded favorably to pyridoxine and that of a third (A.K.), to nicotinic acid. The cheilosis in the fourth and fifth cases (J.M. and M.K.) failed to react satisfactorily to pyridoxine but disappeared while the patient was receiving brewers' yeast. That of the sixth case (F.M.) remained unhealed, even when pyridoxine was employed. In a seventh case (M.J.) a previous trial of nicotinic acid followed by a course of riboflavin was ineffective, and healing did not begin until a low blood ascorbic concentration was raised. In the eighth (M.G.), previous successive courses of pyridoxine and riboflavin administered orally as well as subcutaneously were ineffective, and the cheilosis did not begin to disappear until her scorbutic state was corrected by the administration of vitamin C.

Two of the 3 patients with scurvy have already been referred to; the third one (E.S., Table 2) was more markedly scorbutic. She had the typical manifestations, including a positive tourniquet test. Her blood ascorbic acid level was 0. Her diet consisted only of 16 to 21 bowls of milk and oatmeal daily for a period of 9 months. No manifestations of a B-complex deficiency were noted, but she had at each angle of the mouth a wide fissure which bled freely and the vermilion of her lips was dry, desquamating and oozing blood. The involvement of her lips cleared up entirely within 1 week after the administration of vitamin C.

One patient (A.K.) has already been mentioned as having responded favorably to nicotinic acid, after riboflavin and pyridoxine had been without effect, and another one (G.C.), an alcoholic pellagrin, did likewise. He had, as manifestations of a B-complex deficiency, anorexia, calf muscle tenderness, bilateral symmetrical dermatitis limited to the dorsum of the hands, diarrhea and mental incoherence, and, in addition, on his lower lip a shallow, wide crater resembling an epitheliomatous ulcer, except that there was no induration beneath it. The ulcer healed completely within 5 days after the administration of nicotinic acid.

Recurrence of the cheilotic lesion occurred in 2 of the patients (B.C. and F.R., Table 1). In one of these (B.C.) healing occurred after the daily administration of 30 mg. of pyridoxine for 5 days. Two days later the treatment was stopped, and after another week the lesion had recurred. Again, however, after the daily administration of 30 mg. for a week it subsided and has not reappeared. The other patient (F.R.), with anorexia nervosa, responded satisfactorily to pyridoxine administered subcutaneously for a week, but the lesion reappeared a week after the therapy was abandoned. The

vitamin was then administered orally with no improvement whatsoever; in fact, the lesion became more severe and pustular. It was then discovered that she had been picking at the angles of her mouth with her fingernails, and so perhaps tending to prevent healing.

Comment. That cheilosis frequently subsides during riboflavin therapy appears to be definitely established by several reports in the literature. In some of the cases (Sydenstricker;[10] Oden[5]) the lesion recurs when the administration of riboflavin is discontinued. This may be interpreted to indicate either that a riboflavin deficiency is responsible for the cheilosis or that the administration of riboflavin, which is appetite-restoring in an individual deficient in this vitamin, is accompanied by the consumption of an increased quantity of food and this food contains some substance that brings about healing of the lesion. The latter possibility must always be taken into consideration in connection with the disappearance of a symptom or sign during the administration of a vitamin. At any rate in the present series 8 of the patients treated with riboflavin showed no improvement during its administration, and none of them had any of the other manifestations that characterize the syndrome of ariboflavinosis.

That the administration of pyridoxine also may be followed by a disappearance of the cheilotic lesion is evidenced by the report of Smith and Martin,[7] who noted healing after treatment with this vitamin, and by the observations reported in this paper. That still other members of the B-complex may be responsible is suggested by the observation that in some patients the lesion heals only when the entire B-complex, in the form of liver extract or brewers' yeast, is being supplied.

That a deficiency of cevitamic acid may also be related to the development of cheilosis is suggested by my observations on 3 patients in whom a bleeding lip lesion did not improve until the scorbutic state was brought under control.

Conclusions. The observations herein reported, as well as those of other authors, indicate that cheilosis is not necessarily a manifestation of riboflavin deficiency alone. Healing of the lesion often does not occur when riboflavin only is administered and, on the other hand, it may respond favorably to the administration of pyridoxine and, in some instances, of nicotinic acid. Furthermore, when the lesion is hemorrhagic and is accompanied by generalized involvement of the lips, especially of the vermilion, it may improve only when a low blood ascorbic acid level is elevated.

I am indebted to the chiefs of the medical and dermatologic clinics of the University Hospital and to Drs. Russell S. Boles, Charles L. Brown, Henry D. Jump, Samuel A. Loewenberg, Howard W. Schaffer, and the late Robert G. Torrey of the Philadelphia General Hospital for allowing me to make use of their clinical material for this study.

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A POST-REPEAL STUDY OF 300 CHRONIC ALCOHOLICS.

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Repeal of the 18th Amendment in 1933 was followed by an increase in the number of admissions for chronic alcoholism at the Colorado Psychopathic Hospital. The average for the 2 years, 1931–1932, was 44.5 admissions, and for the 6 years, 1934–1939,

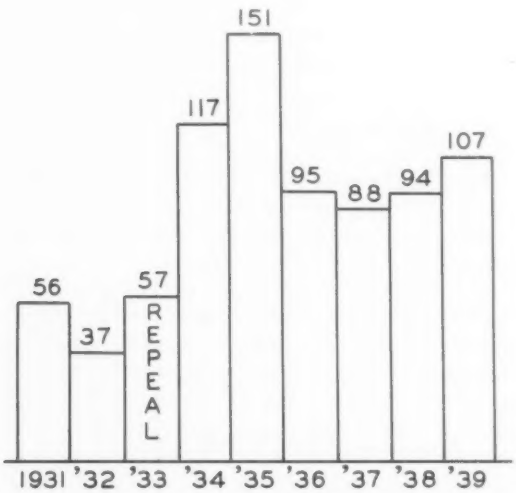


Chart 1.—Yearly admissions for alcoholism at the Colorado Psychopathic Hospital.

it was 107.7. Pollack's[1] figures for chronic alcoholism at the New York State Hospitals showed an average of 596 first admissions in 1931–1932, and an average of 850.4 for 1934–1938. During 1920–1923, a period of effective prohibition in New York, the average

number of first admissions for alcoholism at the same institutions was 204 per year.

The increase in the number of patients admitted for chronic alcoholism at this hospital prompted this investigation. Three hundred patients consecutively admitted during the years 1936–1939 were studied; 38 were readmitted patients. The data presented subsequently are based on this group. The continued use of alcohol was the direct cause of admission in each instance. Most of the patients entered the hospital because of coercion by relatives, and many of them resented being there. Only a few had more than a superficial desire to be rid of their habit. This was evident in their length of stay on first admission—57 (19%) left in less than a week—although an attempt was made not to admit any patient unless the responsible relative understood that a minimum of one month was necessary for any real attempt at therapy.

TABLE 1.—NUMBER OF DAYS IN HOSPITAL ON FIRST ADMISSION.

Days.	No. of patients.
1–7	57
8–14	56
15–21	55
22–28	60
29 or more	72
	300

These patients were quite frank, if not entirely accurate, in their statements regarding the amounts they drank. The preference for whisky was unanimous, but if the financial situation was difficult, a shift to wine occurred. Of these patients 107 (36.3%) were periodic drinkers who would have "sprees" of a week or two of continuous inebreity followed by periods of abstinence lasting from a few weeks to several months.

TABLE 2.—CONSUMPTION OF ALCOHOL.

Whisky:	
Minimum of ½ pint daily	12
Minimum of 1 pint daily	45
Minimum of 1 quart daily	32
Determined by supply	85
Periodic debauches	107
Wine:	
About 1 gallon daily	19
	300

Ninety-eight (32.7%) of the patients were classified as psychotic on admission. The distribution as to type of psychosis is shown in Table 3. Twenty-two (22.4%) of the 98 psychotic patients, and 24 (11.9%) of the 202 patients without psychosis had a peripheral neuritis.

TABLE 3.—TYPE OF ALCOHOLIC PSYCHOSIS ON ADMISSION.

Organic deterioration	44
Delirium tremens	27
Acute hallucinosis	18
Korsakow's psychosis	9
	98

If the consumption of alcohol was enough to produce frequent periods of intoxication or to interfere with the ability to earn a living, it was taken to be greater than social drinking and the individual regarded as a chronic alcoholic. Judged by these criteria, 170 (56.7%) were chronic alcoholics by the age of 30 (Table 4). The average age on first admission was 40 (Table 4). The duration of chronic alcoholism before first admission is shown in Table 5.

TABLE 4.—AGE INCIDENCE OF 300 ALCOHOLICS.

Age group.	At onset.	On first admission.
15–20	65	1
21–30	105	37
31–40	61	104
41–50	32	96
51 or over	16	62
Not given	21	
	300	300

TABLE 5.—DURATION OF CHRONIC ALCOHOLISM PRIOR TO FIRST HOSPITALIZATION.

Less than one year	3
1–5 years	87
6–10 years	61
11–15 years	35
16–20 years	43
21 or more years	51
Not given	21
	300

Information was obtained concerning the level of formal education attained by 273 of the patients; it varied from no school attendance to college graduation. Only 52 (19.1%) of the 273 failed to complete the eighth grade; 122 (44.7%) completed high school; and 41 (15%) attended college. The occupational records of the patients showed frequent changes of employment. Only 32 (10.7%) were able to support their dependents and themselves without receiving aid at intervals. Of the 48 women 36 (75%) were housewives. The distribution by occupation is shown in Table 6.

TABLE 6.—OCCUPATION.

Non-skilled laborers	61	Students	3
Skilled laborers	46	Prostitutes	2
"White collar" workers	39	Gamblers	2
Housewives	36	Bartender	1
Business men	30	Politician	1
Farmers	23	Not given	1
Salesmen	23		
Lawyers, physicians, dentists	11		300
Firemen	6		

The sexual and marital adjustments of these patients were poor. A history of infidelity, impotence, or perversion was obtained in about 150 (50%) of the 300. At the time of admission syphilis was present in 24 (8%), and a history of gonorrhea was given by 49 (16.3%). One hundred and six (41.4%) of the 256 patients who had been married were either divorced or separated, and 12 patients had been divorced more than once (Table 7). Of the 135 patients who were still living with their wives, 48 (35.5%) gave domestic difficulties as the reason for drinking.

TABLE 7.—MARITAL STATUS.

Single	43	Widowed	15
Married	135	Not given	1
Divorced	81		
Separated	25		300

Evidence of poor emotional adjustment was apparent in childhood in 95 (31.7%) of these patients. Sixty-two were "nervous," stubborn, pouty, shy, enuretic, or had night terrors. Twenty-six were over-dependent and carried this through to adult life.

TABLE 8.—CHILDHOOD PERSONALITY TRAITS.

Shy, pouty, "nervous," stubborn	39
Enuretic past the age of 7	18
Night terrors	5
Resented father	7
Unusual parental attachment	26
	95

Ninety patients were associated with chronic alcoholic relatives in early life, and 20 others had suicide deaths or psychotic relatives in the immediate family.

TABLE 9.—FAMILY CHARACTERISTICS.

Patients with alcoholic fathers (48) or mothers (9)	57
Broken home due to separation of parents	35
Rigid, domineering parents	25
Suicide deaths in immediate family	11
Psychotic relatives in immediate family	9
"Nervous" parents	8
	145

Improvement, either from a physical or psychiatric viewpoint or both, was made in 246 (82%). Despite this high percentage of improvement only 18 (6%) had a prognosis on discharge that was considered good, that is, no expectation of relapse. Twenty patients left before any treatment except emergency therapy could be instituted.

TABLE 10.—PROGNOSIS ON DISCHARGE.

Good (no relapse expected)	18
Guarded	137
Poor (relapse expected)	130
Very poor	7
Not given*	7
	299†

* Patients discharged within 24 hours.
† One patient died in the hospital.

An attempt was made to learn the type of adjustment made by these people after their discharge from the hospital. The shortest time from discharge to follow-up was 6 months, the longest 30 months, with a fairly even distribution between these two extremes. The method used for the follow-up was to contact the referring physician or the relative who was responsible for the patient at the time of hospitalization. There are many criticisms of such a method. No information could be obtained about 140 patients; 91 had returned to their pre-hospitalization status; and in so far as could be determined, 60 had not been intoxicated since leaving the hospital.

TABLE 11.—FOLLOW-UP STUDY.

Relapsed	91
No relapse	60
Dead	7
In prison	2
No information	140
	300

Summary. 1. In the 6-year period following the repeal of prohibition (1934–1939), the average number of admissions per year for chronic alcoholism at the Colorado Psychopathic Hospital was 147% higher than the average for the 2 years preceding repeal (1931–1932).

2. One-third of the chronic alcoholics were psychotic on admission. The incidence of peripheral neuritis was 15.3%, with the incidence in the psychotic patients twice as great as in the non-psychotic group.

3. Chronic alcoholism began by the age of 30 in most of the patients, and the average age on first admission was 40.

4. Many patients were reared in family situations complicated by the presence of alcoholic or otherwise inadequate relatives, and showed evidence of poor emotional reactions in childhood.

5. Only 10% were able to make good adult economic and marital adjustments. Of the 256 patients who had been married 41% were either divorced or separated.

6. Most of the patients left the hospital before receiving adequate therapy. Only 6% were given a good prognosis at the time of discharge, although 82% were considered improved by hospitalization.

7. As far as could be determined, 20% of the 300 patients had not been intoxicated for a minimum of 6 months after leaving the hospital. Thirty per cent were known to have returned to their pre-hospitalization status of chronic alcoholism, and no information was obtained on about 47% of the patients.

REFERENCE.

(1.) **Pollack, H. M.**: Psychiat. Quart., **14**, 750, 1940.

BOOK REVIEWS AND NOTICES

FOUNDATIONS OF NEUROPSYCHIATRY. By STANLEY COBB, A.B., M.D., Bullard Professor of Neuropathology, Harvard Medical School; Psychiatrist in Chief, Massachusetts General Hospital. Pp. 231. Second revised and enlarged edition of the work formerly known as A Preface to Nervous Disease. Baltimore: The Williams & Wilkins Company, 1941. Price, $2.50.

THE anatomy, physiology and pathology of the nervous system represent only a means to an end for the majority of students and physicians, namely a way "to understand the simpler workings of the central nervous system" and the reasons for its abnormal reactions. As "only a few simple mechanisms of the nervous system are thoroughly understood," the author wisely decided to "mention only those anatomical structures the physiology of which is known and to discuss only physiological processes for which there is at least a fairly well substantiated anatomical correlation." The choice of the material is free from false respect for time-honored schemes as well as sensational novelties. Clinical requirements have determined the selection of, and ably illustrate, the anatomic and physiologic data discussed in this book. There is no timidity in raising the question of consciousness and unconsciousness or the body-mind problem. No philosophic treatise is given as solution but appropriately simplified considerations are offered to the reader. Obsolete antitheses such as "organic-functional diseases" and "physical-mental phenomena" are forcefully attacked and placed in correct perspective.

The author believes "that Sherrington's idea of integration gives a working hypothesis upon the basis of which one may be eventually able to explain the higher mental functions." He does not hesitate to state his personal opinion in such controversial questions as cortical localization *vs.* function of the brain as a whole.

The book opens with the discussion of structure and function of the autonomic nervous system and its importance for internal medicine as well as for neurology and psychiatry. The antagonistic mechanism of micturition is clearly exposed and the interaction of fear, tachycardia, increased blood pressure, goose-skin, etc., exhibited. The presentation of segmental and suprasegmental apparatus in the central nervous system includes the reflex mechanisms of spinal cord and brainstem, the functions of the cranial nerves, the respiratory and equilibratory systems, pathways and rôle of exteroceptive and proprioceptive stimuli and their integration in cerebellar and cerebral cortex.

The succeeding chapters deal with motor integration, locomotion, and functional localization in the cerebral cortex. The old and new motor system and the action of the basal ganglia in contrast to the cortex are stated and the various levels of posture and locomotion described. The confused anatomic nomenclature of the basal ganglia is clarified by the help of a table, and the meaning of such debatable designations as rigidity and spasticity is clearly outlined. The different function, *e. g.*, of area 6 or of the cerebellum, in man and laboratory animals below apes is correctly stressed. Consciousness is defined as "a function of the organism in action." Under the title of unconsciousness, on the other hand, the problem of syncope is debated and the rôle of hemodynamics, blood chemistry and blood oxygen content in it. This leads to the excellent chapter on

cerebral circulation. The principal reflex arcs are shown controlling the bloodflow to the brain, comprising the carotid and aortic bodies, the cardiac, arterial and venous, pressure and chemical receptors, the angiospastic and vasodilating action, and the intracerebral control of bloodflow, the metabolic exchange between blood and tissue in the capillaries, and the lesions caused by oxygen deprivation.

Special chapters are dedicated to the spinal fluid, the general and special pathology of the peripheral and central nervous system. Epilepsy is treated not as a disease but as a pathophysiologic phenomenon, characterized by dysrhythmic brain waves. Its importance as a Public Health problem is exemplified by the statement that 650,000 persons in the United States are assumed to suffer from periodic seizures.

The last chapter, giving an introduction into psychopathology, calls for a broader approach to this problem. "There are psychiatrists who state that neurology can contribute nothing to their field; there are psychoanalysts who are interested only in 'interpersonal relations' and know nothing of the brain; there are neurophysiologists who deny psychology and consider analysis a 'racket.' What is important . . . . is better training for everyone in all four fields and more tolerance. . . ."

The book is informative and stimulating and is highly recommended to medical students and physicians as well as to all instructors of biology and psychology. F. L.

TECHNIQUES OF CONCEPTION CONTROL. By ROBERT LATOU DICKINSON, M.D., Former President, American Gynecological Society, and WOODBRIDGE EDWARDS MORRIS, M.D., General Medical Director, Birth Control Federation of America. Pp. 56; 50 illustrations. Baltimore: The Williams & Wilkins Company, 1941. Price, 50c.

IN a world of rapid change both socially and economically, an increasing interest and demand on the part of Society is developing in the matter of controlling reproduction so that the timing of pregnancies may be planned. Under such conditions marriage can take place earlier, and family size can be regulated according to the ability of the parents to give their children an adequate start in life.

For the proper regulation of reproduction the medical profession needs to be acquainted with the various methods that are effective. This is important as a single method is not necessarily suitable for every individual. Dickinson and Morris have produced a manual describing the various methods now in use, which should be in the hands of every physician who desires to fulfill his obligation to the patient needing such help. The subject is fully covered and its value greatly enhanced by a series of 50 excellent illustrations. D. M.

BRUCELLOSIS (Undulant Fever). Clinical and Subclinical. By HAROLD J. HARRIS, M.D., Health Officer, Westport, N. Y.; Consulting Physician, St. Lawrence State Hospital; Attending Physician, Elizabethtown Community Hospital, etc. Foreword by WALTER M. SIMPSON, M.D., F.A.C.P., Director, Kettering Institute for Medical Research, Miami Valley Hospital, Dayton, Ohio. Pp. 286; 44 text illustrations and 12 in color. New York: Paul B. Hoeber, Inc., 1941. Price, $5.50.

ONLY 17 years have passed since the first proven case of human brucellosis of bovine origin was reported. Yet the writings of a few observers, including the author of this volume, have aroused an increasing awareness on the part of physicians of the widespread prevalence of this disease, with the result that several thousands of cases have been recognized yearly during the past

decade. For the most part these have been examples of the more acute forms of the disease. But recent clinical experience shows that chronic brucellosis is even more common, and constitutes a major cause of chronic ill health. Since the available information on brucellosis is restricted almost wholly to journal articles, the publication of a monograph on the subject is timely. It is therefore all the more regrettable that the book is open to a number of serious criticisms. In his enthusiasm to present the manifold clinical aspects of chronic brucellosis, the author has fallen into the very error which he says he wishes to avoid; that of attributing to brucellosis, without adequate proof, certain symptoms and findings that happened to be encountered in patients with chronic brucellosis. Examples are: duodenal ulcer; glycosuria; borborygmus; hematuria; alveolar abscess in 75% of cases (one patient had 28 abscessed teeth, but cultures were negative); sinusitis (usually frontal, "a frequent finding" in patients with chronic brucellosis); thyrotoxicosis. The factor of a non-specific protein shock effect is at times underestimated, as in deprecating the value of intravenous typhoid therapy in acute brucellosis recently acquired; at times overlooked, as in attributing too great a diagnostic significance to the response to brucella vaccine treatment in doubtful cases. The discussion of the control of the disease in lower animals, especially the problems presented by the infection in range cattle and in other animals, is inadequate. While the literature has been sufficiently covered, there is failure at times critically to evaluate much that has been included. Nevertheless, the book contains a wealth of useful information. Particularly well done are the description and interpretation of the various diagnostic tests and the discussion of the use of brucella vaccine in the treatment of chronic brucellosis. R. K.

CLINICAL PELLAGRA. By SEALE HARRIS, M.D., Professor Emeritus of Medicine, University of Alabama, Birmingham, Assisted by SEALE HARRIS, JR., M.D., Formerly Assistant Professor of Medicine, Vanderbilt University, Birmingham, Ala. With a Foreword by E. V. MCCOLLUM, PH.D., SC.D., LL.D., Professor of Biochemistry, School of Hygiene and Public Health, The Johns Hopkins University, Baltimore. Pp. 494; 66 illustrations and 16 tables. St. Louis: The C. V. Mosby Company, 1941. Price, $7.00.

IT is a decided advantage to have an adequate description of so important and widely distributed a disease as pellagra presented in a single ready reference volume. McCollum in his introduction to the work, calls attention to the thread of etiologic philosophy and reflective comment on which the author has strung both clinical observation and literature, and rightly estimates this as an attraction and asset of the work, though perhaps in these days a bit of a space-consuming luxury.

The text covers history and epidemiology (3 chapters); historical review of causal investigation and theory (6 chapters); etiology and pathology (5 chapters); clinical investigations (3 chapters); symptomatology, diagnosis and prognosis (8 chapters); prophylaxis (3 chapters); treatment (3 chapters); bibliography circa, 600 titles; index, 21 pages.

Obviously a book of this scope will contain much for the expert in the fields which pellagra invades through its varied symptomatology, cutaneous gastro-intestinal, neurologic. The author has succeeded in maintaining a central thesis without reducing his presentation to polemic or propaganda. The cause of pellagra, or better the complete causal mechanism of pellagra is still unknown, and is probably an interplay of predisposing and exciting causes. The former include alcohol, corn toxins, gastro-intestinal infections or infestations, carcinoma and other chronic gastro-intestinal diseases. The latter include avitaminosis—nicotinic acid deficiency especially; defi-

ciency of the "gastric intrinsic factor;" liver disease or inadequacy resulting in inability to store or utilize nicotinic acid; and sunlight (photosensitiveness). Harris' suggestions for experimental studies indicate the emphasis he places on gastro-intestinal and liver malfunction, the importance of bacteriologic and mycologic studies of pellagrous diets and the metabolism of coproporphyrin in relation to nicotinic acid utilization and deficiency.

In the body of the text the clinical delineation and differentiation of the typical "3 D" (dermatitis, diarrhea, dementia) pellagra, and the various atypical or what one might call the parapellagra manifestations, is well handled. The emphasis on endemic character and national and world-wide distribution is still timely. Treatment is dealt with with the sure touch of experience and much interesting detail. The recommended dosage of nicotinic acid (100 mg. daily at one point) seems small. The interrelations of sprue, pernicious anemia and pellagra are constructively used in integrating the multiple causal concept to which the author gives his support.

The presswork is excellent, the photography fair (some badly focussed subjects), the color plate of the pellagrous tongue the best the Reviewer has seen, though too much reduced. A close-up showing the detail of the highly characteristic keratotic or steatotic "saddle" over nose and cheeks would be a useful inclusion in a future edition. The price of the work is too high considering its value to the large number of physicians who could and should use it. J. S.

PHYSICAL MEDICINE. The Employment of Physical Agents for Diagnosis and Therapy. By FRANK H. KRUSEN, M.D., F.A.C.P., Associate Professor of Physical Medicine, the Mayo Foundation, University of Minnesota; Head of the Section on Physical Therapy, the Mayo Clinic, etc. Pp. 846; 351 illustrations. Philadelphia: W. B. Saunders Company, 1941. Price, $10.00.

THIS work, as stated in the preface, "has been written with the purpose of presenting in one volume the modern concepts of the subject of physical medicine." The book fills a crying need because, to quote again the author, "Although there are excellent books available which deal with one or two branches of the subject, as well as good large reference works, there is, perhaps, no other book which covers the whole subject in a way that has been attempted herein."

The author has been successful in attaining his purpose. All the various disciplines of physical medicine are presented in this work in a well-balanced form in one single volume and discussed in an authoritative manner, the book showing throughout evidence of having been written by a master in his field. The text is based essentially on the author's original studies and clinical experience, but also includes a great number of observations taken from other well-selected sources. To these sources detailed reference is given at the end of each chapter. Throughout the text the various phases of the subject matter are critically analyzed and evaluated. Polemic topics are presented, discussed impartially, the author frequently expressing his own opinions. These opinions are amplified by numerous case reports, graphs, and statistical data. As stated in the preface, "Throughout the text, particular emphasis has been laid on the simple physical measures which are readily adaptable for general practice."

The subject is divided into 9 parts. The first deals with the history of physical therapy. The next 5 parts are devoted to a discussion of the various branches of physical therapy according to the particular agent employed, namely, thermotherapy, light therapy (a particularly informative part of the book), electrotherapy, hydrotherapy, and mechanotherapy. Part VII treats of the clinical aspects of physical medicine with emphasis laid on physical therapy of arthritis, the relation of physical therapy to

orthopedic surgery and to its management of backache. The remaining 2 parts deal with the teaching of physical medicine and with the hospital department of physical therapy. The index is complete.

The reading of this volume should be of much benefit not only for the physical therapist, but also for specialists in other fields of medicine, as well as for the general practitioner. J. N.

MEDICAL MANUAL OF CHEMICAL WARFARE. (First American Edition; Reprinted by Permission of The Controller of his Britannic Majesty's Stationery Office.) Pp. 119; 1 figure and 10 plates. Brooklyn: Chemical Publishing Company, Inc., 1941. Price, $2.50.

THE first American reprint of this British publication will be welcomed as a valuable text for physicians who, as civilians or as officers in the armed forces, may be required to handle the casualties resulting from chemical warfare. Chapter headings include: General description of war gases; the vesicant or "blister" gases; the lung irritant or choking gases; paralysant gases; arseniuretted hydrogen poisoning; gases used primarily as harassing agents; dangerous gases not used for offensive purposes, but which may be encountered under war conditions; protection against gas and air raids; the recognition and first aid treatment of "gas casualties." There are appended a tabular summary of gases, their properties, methods of recognition and first-aid treatment; a description of the technique of administration of oxygen; and the "Atlas of Gas Poisoning": a 15-page reprint, with 10 illustrations, of a pamphlet first used in 1918 by the Medical Research Committee. The presentation is concise, correct and adequate for practical purposes. As set forth in the foreword, "It cannot be too strongly emphasized that a speedy recognition of the type of gas which has caused casualties is essential for rapid diagnosis and treatment: these desiderata can only be obtained by timely and thorough knowledge of chemical warfare substances, their characteristics, and their effects on the human body." This volume fully meets the issue. R. K.

BIOLOGY OF THE LABORATORY MOUSE. By the Staff of The Roscoe B. Jackson Memorial Laboratory, CLARENCE C. LITTLE, Director, GEORGE D. SNELL, Editor, J. J. BITTNER, A. M. CLOUDMAN, E. FEKETE, W. E. HESTON, W. L. RUSSELL, G. W. WOOLLEY. With a Chapter on Infectious Diseases of Mice by J. H. DINGLE, Harvard Medical School. Pp. 497; 172 illustrations. Philadelphia: The Blakiston Company, 1941. Price, $7.00.

To indicate the purpose of this book it is difficult to improve upon statements in the preface: "Of all the laboratory mammals, probably none has contributed more to the advancement of knowledge than the common mouse. . . . . A result of this extensive use of the mouse is . . . . a large body of information . . . . so widely scattered that it is often a major undertaking for the research worker who wishes to use it to locate and gather the particular facts that he needs. Much of this information is assembled in this book. In a number of cases . . . . important gaps in the literature . . . . have been filled in by special research projects. . . . . Because it deals with the mouse alone, this book presents a vertical cross-section of biological knowledge rather than the more usual horizontal cross-section."

The book contains the following chapters, prepared as indicated by various authors, which with one exception are members of the staff of the Jackson Laboratory: 1, The Early Embryology of the Mouse; 2, Repro-

duction; and 5, Gene and Chromosomes Murations—G. D. SNELL; 3, Histology—ELIZABETH FEKETE; 4, Spontaneous Neoplasms in Mice—A. M. CLOUDMAN; 6, The Genetics of Spontaneous Tumor Formation; and 7, The Genetics of Tumor Transplantation—C. C. LITTLE; 8, Endocrine Secretion and Tumor Formation—G. W. WOOLLEY; 9, The Milk Influence in Tumor Formation; and 13, Care and Recording—J. J. BITTNER; 10, Inbred and Hybrid Animals and Their Value in Research—W. L. RUSSELL; 11, Parasites—W. E. HESTON; 12, Infectious Diseases of Mice—J. H. DINGLE.

The text is abundantly illustrated by drawings, photomicrographs and charts. An extensive bibliography is appended to each chapter. The index is entirely adequate. The editor and authors of the various chapters are to be congratulated. All who use the laboratory mouse must feel a distinct obligation to them. H. R.

PLAY FOR CONVALESCENT CHILDREN IN HOSPITALS AND AT HOME. By ANNE MARIE SMITH (Staff Instructor), Leaders' Training School, Community Recreation Service, Chicago, Ill. Pp. 133. New York: A. S. Barnes & Co., 1941. Price, $1.60.

THIS small book outlines the growth of organized play on the wards of the Children's Memorial Hospital in Chicago. It is, however, a good deal more than that. It is convincing evidence of the value of intelligently organized play as an essential part of the treatment of sick children and as such should be required reading for a great many doctors, nurses and hospital administrators.

There is a brief but good discussion of the types of play suitable to varying types of situations such as that of the general ward, isolated, chronically ill, and preoperative patient. The references to more detailed special works and the list of suitable and popular books for the library are very helpful. S. L.

CONDITIONED REFLEXES AND PSYCHIATRY (Vol. 2 of Lectures on Conditioned Reflexes). By IVAN PETROVITCH PAVLOV, Late Director, Physiological Laboratories, Institute of Experimental Medicine and Academy of Sciences, Leningrad; Late Professor of Physiology, Military Medical Academy, Leningrad, etc. Translated and Edited by W. HORSLEY GANTT, M.D., B.Sc., Medical Director, Leningrad Unit American Relief Administration, 1922–23; Coworker in Pavlov's Laboratory, Institute of Experimental Medicine, 1925–29; Associate in Psychiatry and Director Pavlovian Laboratory, Johns Hopkins University. Vol. 1, with the collaboration of G. VOLBORTH, M.D., Former Assistant to Professor Pavlov at the Military Medical Academy; Professor of Physiology, University of Kharkov, and an Introduction by WALTER B. CANNON, M.D., S.D., George Higginson Professor of Physiology, Harvard University. Pp. Vol. 1, 414; Vol. 2, 199. Illustrations, Vol. 1, 9; Vol. 2, 7. New York: International Publishers, 1941. Price, Vol. 1, $3.50; Vol. 2, $4.00.

FOR those who have read "Conditioned Reflexes, An Investigation of the Physiological Activity of the Cerebral Cortex," the present volume suffers by comparison. The former book is a clear, systematic presentation of an important series of researches. It includes speculation of which the validity may at times be questioned, yet always supported by impressive experimental evidence.

"Conditioned Reflexes and Psychiatry" is a collection of lectures obviously never planned as a series. Since each was delivered to a different audience, the introductory résumé of earlier work, essential in presentation

from the platform, becomes tedious to the reader through recurrence. Too seldom has the translator deleted such material. He has preferred literal rendition to clarity and grace of style. The admirable introduction bears ample internal evidence that the choice was imposed solely by reverence for the author. It will be deprecated by the reader primarily concerned with the subject; yet appreciated for retaining the full flavor of the vivid personality of the great physiologist.

A more serious stricture is the almost complete absence of protocols, such as those which formed the backbone of the earlier book. Instead a relatively small number of experimental results are offered in support of a superstructure of theory which totters perilously far from its foundations.

G. McC.

Optical Activity and Living Matter. (No. 2 of a series of Monographs on general physiology, edited by B. J. Luyet). By G. F. Gause, Professor of Experimental Biology, University of Moscow. Pp. 162; 18 illustrations. Normandy, Mo.: Biodynamica, 1941. Price, $2.75.

An editorial preface to this second in a series of monographs on general physiology ventures the suggestion that the optical activity of living material has not received attention among American biologists commensurate with its importance. The author has summarized adequately and completely the imposing literature on the structure and activity of living systems as related to the asymmetric configuration of their constituents. Fundamental questions concerning the origin, maintenance and inheritance of the so-called "natural" stereoisomers are presented concisely and speculated upon with a refreshing clarity obscured only infrequently by the author's apparent teleology.

The book is of value to biologists, physiologic chemists, and those engaged in fundamental medical research. Practicing physicians will find it readable, absorbing and informative; particularly will they appreciate the concise, restrained manner in which Professor Gause has presented the background of the recent controversy concerning the reported appearance of unnatural isomers in neoplasms. It is unfortunate that this definite contribution to our biologic literature will probably not receive the audience it deserves.

L. C.

Accidental Injuries. The Medico-Legal Aspects of Workmen's Compensation and Public Liability. By Henry H. Kessler, M.D., Ph.D., F.A.C.S., Medical Director, New Jersey Rehabilitation Clinic; Formerly Medical Adviser, New Jersey Workmen's Compensation Bureau, etc. Pp. 803; 202 illustrations. Second Edition, enlarged and thoroughly revised. Philadelphia: Lea & Febiger, 1941. Price, $10.00.

This book, which first appeared in 1931, is thoroughly revised in this edition. It is written from the point of view of a compensation administrator. In the first portion of the book, he has brought up to date the comparison of the various compensation laws as they relate to medical and hospital services. It is interesting to note that for every dollar paid for compensation and handled by stock companies, 42 cents goes to the carrier, 38 cents for cash compensation, and 20 cents for medical and hospital services.

Included in the book are many diagrams which serve to show at a glance the subject which the author wishes to emphasize. A very thorough section is given on examination and estimation of disability. A new chapter on the eye has been added by Dr. A. Rados.

This book, written largely by one man, is a statistical compilation and a

résumé of experience in the relation of accidental injuries to disease. It should prove extremely valuable to physicians doing compensation work, to insurance carriers, to compensation lawyers and to others interested in the relation of injury to disease. L. F.

NEW BOOKS.

Functional Pathology. By LEOPOLD LICHTWITZ, M.D., Chief of the Medical Division of the Montefiore Hospital; Clinical Professor of Medicine, Columbia University. Pp. 567; 157 illustrations. New York: Grune & Stratton, Inc., 1941. Price, $8.75.

The Retina. The Anatomy and the Histology of the Retina in Man, Ape, and Monkey, Including the Consideration of Visual Functions, the History of Physiological Optics, and the Histological Laboratory Technique. By S. L. POLYAK, M.D. A Fiftieth Anniversary Publication of The University of Chicago Press. Pp. 607; 100 illustrations (1 in color). Chicago: The University of Chicago Press, 1941. Price, $10.00.

The Proceedings of The Charaka Club. Volume X. Post Multa Virtus Opere Laxare Solet. Pp. 260; illustrated. Baltimore: The Williams & Wilkins Company, 1941, for The Charaka Club. Price, $5.00.

Eye Hazards in Industry. Extent, Cause and Means of Prevention. By LOUIS RESNICK. Pp. 321; 33 illustrations. New York: Columbia University Press, 1941, for National Society for the Prevention of Blindness. Price, $3.50.

From Cretin to Genius. By DR. SERGE VORONOFF. Pp. 281. New York: Alliance Book Corporation, 1941. Price, $2.75.

Nutritional Deficiencies. Diagnosis and Treatment. By JOHN B. YOUMANS, A.B., M.S., M.D., Associate Professor of Medicine and Director of Post-Graduate Instruction, Vanderbilt University Medical School, Nashville. Assisted by E. WHITE PATTON, M.D. Pp. 385; 14 illustrations. Philadelphia: J. B. Lippincott Company, 1941. Price, $5.00.

Better Nursing for America. By BEULAH AMIDON. (Public Affairs Pamphlet, No. 60, 1941.) Pp. 32; illustrated. New York: Public Affairs Committee, Inc., 1941. Price, 10c.

Sex Life in Babylonia. By EDWIN W. HIRSCH, M.D. (From the Urologic and Cutaneous Review, Sept., 1941.) Pp. 38. Chicago: Research Publications, 1941.

Sinus. By RUSSELL CLARK GROVE, M.D. Pp. 188; 16 illustrations. New York: Alfred A. Knopf, 1941. Price, $2.00.

The Man Who Lived for Tomorrow. A Biography of William Hallock Park, M.D. Pp. 507; 1 illustration. New York: E. P. Dutton & Co., Inc., 1941. Price, $3.75.

Pneumoconiosis (Silicosis). The Story of Dusty Lungs. A Preliminary Report. By LEWIS GREGORY COLE, M.D., Director of Silicotic Research, John B. Pierce Foundation, New York City, and WILLIAM GREGORY COLE, M.D., New York City. Pp. 21; illustrated. New York: John B. Pierce Foundation, 1940.

The Value of Health to a City. Two Lectures Delivered in 1873 by MAX VON PETTENKOFER. Translated from the German, with an Introduction by HENRY E. SIGERIST. Pp. 52; 1 illustration. Baltimore: The Johns Hopkins Press, 1941. Price, $1.00.

A reprint (Bull. Hist. Med., **10**, 473, 1941) of two of Pettenkofer's lectures that were important in advancing the subjects of modern public health and medical economics.

Social Influences Affecting the Behavior of Young Children. By RUTH PEARSON KOSHUK. (Volume VI, No. 2, Serial No. 28.) *The Hearing of School Children.* A Statistical Study of Audiometric and Clinical Records. By ANTONIO CIOCCO, and CARROLL E. PALMER, Division of Public Health Methods, National Institute of Health, Bethesda, Md. (Volume VI, No. 3, Serial No. 29.) (Monographs of the Society for Research in Child Development.) No. 28, 71 pages; No. 29, Pp. 77; 14 figures and 40 tables. Washington, D. C.: Society for Research in Child Development, National Research Council. Price, $1.00 each.

Xanthoma and Other Dyslipoidoses. By FRED D. WEIDMAN, M.D., L. NAPOLEON BOSTON, M.D., JOSEPH STOKES, JR., M.D., HOWARD W. SCHAFFER, M.D., WALTER FREEMAN, M.D., and F. W. SUNDERMAN, M.D., Philadelphia. Pp. 195; illustrated. Philadelphia: University of Pennsylvania Press for the Authors, 1941. Price, $3.00.

The Medical Clinics of North America, Volume 25, No. 6, November, 1941. Military Medicine. Three Year Cumulative Index, Volumes 23, 24 and 25 (1939, 1940 and 1941). Pp. 417; 49 illustrations. Philadelphia: W. B. Saunders Company, 1941.

NEW EDITIONS.

Infant Nutrition. A Textbook of Infant Feeding for Students and Practitioners of Medicine. By WILLIAMS MCKIM MARRIOTT, B.S., M.D., Late Professor of Pediatrics, Washington University School of Medicine; Physician in Chief, St. Louis Children's Hospital. Revised by P. C. JEANS, A.B., M.D., Professor of Pediatrics, College of Medicine, State University of Iowa, Iowa City. Pp. 475; 31 illustrations. Third Edition. St. Louis: The C. V. Mosby Company, 1941. Price, $5.50.

Diseases of Women. By HARRY STURGEON CROSSEN, M.D., F.A.C.S., Professor Emeritus of Clinical Gynecology, Washington University School of Medicine; Gynecologist to the Barnes, St. Louis Maternity and St. Luke's Hospital, etc., and ROBERT JAMES CROSSEN, A.B., M.D., Assistant Professor of Clinical Gynecology and Obstetrics, Washington University School of Medicine; Assistant Gynecologist and Obstetrician to the Barnes and the St. Louis Maternity Hospitals, etc. Pp. 948; 1127 illustrations, many in color. Ninth Edition, entirely revised and reset. St. Louis: The C. V. Mosby Company, 1941. Price, $12.50.

Medical Diseases of War. By SIR ARTHUR HURST, M.A., D.M. (OXON.), F.R.C.P., Lieutenant-Colonel, Late R.A.M.C.; Lecturer on Clinical Medicine, University of Oxford, and Consulting Physician to Guy's Hospital, etc. With the coöperation of H. W. BARBER, M.A., M.B. (CANTAB.), F.R.C.P., Physician-in-Charge of the Skin Department, Guy's Hospital, H. B. F. DIXON, M.C., M.D. (DUB.), D.T.M. AND H., F.R.C.P., Lieutenant-Colonel (temporary Colonel), R.A.M.C., F. A. KNOTT, M.D. (LOND.), M.R.C.P., Bacteriologist to Guy's Hospital. T. A. ROSS, M.D. (EDIN.), F.R.C.P., Late Medical Director of Cassel Hospital for Functional Nervous Disorders, and ARNOLD W. STOTT, M.A. (CANTAB.), F.R.C.P., Colonel, R.A.M.C., Late Consulting Physician to the British Expeditionary Force; Physician to Westminster Hospital. Pp. 427; 48 illustrations. Second Edition. Baltimore: The Williams & Wilkins Company, 1941. Price, $5.50.

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE.

UNDER THE CHARGE OF
JOHN H. MUSSER, M.D.,
PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA, NEW ORLEANS.

GLOMERULONEPHRITIS.

Limitations. The investigations of Bright, Volhard and Fahr, Addis and many others have established the clinical and pathologic features that characterize the entity called variously glomerulonephritis, hemorrhagic nephritis or hemorrhagic Bright's disease. These features are too well known to require further elaboration. Although the picture as a whole is generally agreed upon, unanimity of opinion is not complete as to the precise criteria for diagnosis either pathologically or clinically. By means of special stains, Bell[13a] has observed swelling of glomerular endothelium in kidneys from patients dying as a result of a great variety of diseases, and is led thus to conclude that there is no sharp histologic distinction between subclinical and clinical acute glomerulonephritis. From the clinical standpoint, Murphy and Rastetter[54] have stated that if the classic textbook picture of hematuria, hypertension and edema is regarded as essential for a diagnosis of acute nephritis, then many milder forms will pass unrecognized, and not until years later when chronic nephritis has set in will the true significance of the mild early episode become apparent. These authors followed the course of 150 patients diagnosed as having acute glomerulonephritis on the basis of albumin, red blood cells, casts and pus cells in the urine for one week or more, without necessarily having edema, azotemia or hypertension. The high incidence of unfavorable outcome (15.3% died, 35.3% became chronic) is evidence of the seriousness of the renal lesion in these patients. Some doubt has also been cast on the existence of the benign type of nephritis known as acute focal glomerulonephritis. According to Volhard and Fahr, this type of nephritis is a symptomless hematuria, occurring at the height of an acute infection, without edema, azotemia, hypertension or oliguria, and with a uniformly good prognosis. In a careful long-term study of more than 300 cases of nephritis in childhood, Payne and Illingworth[60] were unable to distinguish between focal and diffuse acute glomerulonephritis on the basis of the criteria mentioned.

Baehr,[9] on the other hand, regards the viewpoint of Bell as a misinterpretation of a common postmortem finding analogous to the clinical error of diagnosing glomerulonephritis merely because of the presence of albumin and casts or of red blood cells in the urine. He believes: 1, that glomerulonephritis in its acute form is a sharply circumscribed entity; 2, that it is part of a disease of the body as a whole; 3, that its clinical manifestations can be related to characteristic pathologic phenomena in various parts of the body; and 4, that the disease has a specific etiology and pathogenesis.

As regards the relationship of nephrosis to nephritis, controversy continues between the two schools of thought.[28]

Pathogenesis. The types of infection preceding the onset of acute glomerulonephritis in 976 cases collected from the literature[38] are as follows: sore throat, and tonsillitis, 32.1%; upper respiratory infection, 24.4%; scarlet fever, 6.4%; otitis and sinusitis, 5.7%; skin infections, 4.1%; pneumonia, 4%; rheumatic fever, 1.7%; miscellaneous, 10.3%; and infection unknown, 11.3%. Thus, infections of the upper respiratory tract including scarlet fever account for 69% of the cases.

Although other organisms such as the pneumococcus[15,67] and *Streptococcus viridans*[9] have been related to the etiology of acute glomerulonephritis, in most instances the hemolytic streptococcus has been incriminated. Not only have increased titers of antistreptolysin been found in serum,[45a,48] but in one series[45b] this organism has been recovered by culture in 90% of cases. Furthermore, there is evidence that the streptococcal infections preceding glomerulonephritis are usually of the "deep" type[55] in at least two-thirds of the cases,[68] as opposed to the superficial type of infection preceding rheumatic fever.

The exact manner in which the hemolytic streptococcus produces its effect on the kidney has not been established. The studies which may throw some light on this question have been reviewed by Longcope.[45b] There is no evidence to show that the lesions are set up by direct infection of the kidneys, nor exclusively by the action of toxins. The interval of time between the onset of infection and the appearance of the first symptoms of nephritis varies from 3 to 28 days, the average falling on the tenth or eleventh day. This latent period suggested to Schick and to others a similarity to the incubation period of serum disease. Furthermore, following exacerbations of glomerulonephritis, this prodromal period is shortened to a few days,[45b,69] calling to mind the accelerated reaction following a second injection of serum. Baehr[9] has pointed out that, in subacute bacterial endocarditis due to the *Streptococcus viridans*, some immunologic reaction is necessary for the production of nephritis. Whereas, true diffuse nephritis is seldom seen in cases that have remained bacteriemic until death, $33\frac{1}{3}$% of those patients who have killed off their bacteria and entered the bacteria-free stage die as a result of typical diffuse glomerulonephritis.

In the past many investigators have attempted to reproduce glomerulonephritis in experimental animals by the use of streptococci or their products. The results have not been consistent and where nephritis has been produced it has not borne close resemblance to the disease in humans. The type of glomerulonephritis which at present is receiving most attention is that obtained by the injection of nephrotoxic sera. Introduced by Lindeman in 1900, this method has recently

been studied in the rabbit by Masugi and others,[8,41a] in the rat,[71] and in the dog.[17,25] Organ-specific antiserum is prepared in another species (duck, hen, and so on) by injections of perfused and washed kidney tissue of the test species, and subsequently injected into the test animal. After a latent period which is short for the rat but longer for the rabbit and dog, renal injury becomes evident, and with repeated injections may progress fatally. Although it has been stated[17] that nephrotoxic nephritis is a true antigen-antibody reaction and not due to antibodies to blood proteins, Kay[41b] has presented evidence indicating that this simple explanation is insufficient and that an immune response to the donor's serum also plays a rôle. He found that inhibition of these antibodies by Roentgen irradiation prevented the nephritis, whereas prior injection of donor serum accelerated the reaction.

The studies mentioned above have all involved nephrotoxic sera produced in a heterologous species. Schwentker and Comploier,[66] employing the method of Burky[19] for rendering homologous organs antigenic, have produced antikidney antibodies in rabbits by the injection of homologous kidney to which streptococcic toxin had been added. Having shown that homologous antikidney antibodies could be produced in the experimental animal, these investigators tested the sera of humans and found antibodies to rabbit kidney in 92% of patients with scarlet fever as against only 10% in normals. This suggests the possibility that, as a result of scarlet fever, patients may develop antibodies to their own kidneys. It is of interest at this time to recall that whereas full-blown glomerulonephritis is said to follow in less than 5% of cases of scarlet fever,[38] Lyttle[47a] has demonstrated by the Addis technique[1a] that many patients during recovery from scarlet fever show a transient but often significant increase in the excretion of albumin, casts, leukocytes and red blood cells in the urine.

The production of glomerulonephritis in rats by the subcutaneous injection of plasma, serum or their ultrafiltrates from patients with glomerulonephritis has been reported by Schober,[65] and interpreted by him as demonstration of a toxic principle which is the cause of glomerulonephritis.

A consideration of certain biologic differences between glomerulonephritis and rheumatic fever has been presented by Seegal and Earle.[68] Their summary is as follows: 1, Although both diseases appear to be initiated by Group A hemolytic streptococcal infection, the geographic incidence of acute glomerulonephritis is similar for all latitudinal regions in North America, whereas the incidence of rheumatic fever is less frequent in the southern than in the northern latitudinal regions of North America. 2, Although twice as many males as females contract glomerulonephritis, this sex variation is not apparent in rheumatic fever. 3, The preceding clinical infection in acute glomerulonephritis is a "deep" hemolytic streptococcal infection in at least two-thirds of the cases, in contrast to the usual superficial pharyngitis preceding the onset of rheumatic fever. 4, There is a distinct shortening of the latent period following infection in the exacerbations of chronic nephritis, as compared with that in acute glomerulonephritis. This shortening of the latent period in exacerbation or relapse is absent in rheumatic fever. 5, Relapse, while a rarity following the healed state of acute glomerulonephritis, is a common if not regular occurrence following the rheumatic episode.

Pathologic Anatomy. Dissatisfied with the two-dimensional picture of the pathologic anatomy of chronic Bright's disease as revealed in histologic sections, Oliver has undertaken a study in three dimensions by the methods of: 1, micro-dissection, and 2, the construction of models from serial sections. The results of his long and fruitful labors are published in a beautifully illustrated monograph.[58] There appears to be a striking similarity in the architecture of all forms of contracted kidneys no matter what combination of initial processes has produced the ultimate deformity. The alterations in structure involve the nephron, the vascular system and the interstitial tissue. As regards the nephron, two forms are predominant, the hypertrophic and the atrophic, although a single nephron may show either of these processes in different areas along its length. The hypertrophic nephron is characterized by marked hypertrophy and hyperplasia of the proximal convolution, especially in its terminal segment. The increase in relative volume may become as high as 10 times the normal. The glomeruli of such tubules may be decreased in size or, indeed, absent, as in the nephrons of the aglomerular kidneys of certain fish. Even in these aglomerular tubules, the cells retain the morphology of functioning cells, and differ greatly from the flattened cells of tubules that are passively dilated as a result of obstruction distally. The author is extremely cautious in interpreting the significance of these hypertrophied proximal convolutions, but increased function seems likely. The structure of the atrophic nephron is less complex, there being general reduction in size of all parts. In addition to aglomerular tubules, atubular glomeruli are found, and there may be interruptions of the continuity of the nephron at other points along its course, with apparent survival of the segments. The distal convolution as a result of its functional and structural characteristics is the site of early occlusion with débris and, by this stoppage, it may become the point of origin of a distortion of the entire nephron.

The transformation of the architecture of the arterial tree is equally profound. The well-known changes in the afferent arterioles and the glomerular capillaries are evident, but there is an alteration of even greater significance involving Ludwig's vessel. This vessel, arising from the afferent arteriole, serves to shunt blood directly to the peritubular capillary plexus, avoiding passage through the glomerulus. Whereas in the normal kidney Ludwig's vessels are few in number, they are found with significant frequency in all forms of terminal Bright's disease. The demonstration of this compensatory blood supply to the tubules in kidneys in which the glomerular capillary bed has been blocked appears to solve a problem that has long taxed the ingenuity of pathologists.

Judging from the architectural pattern of the contracted kidney of Bright's disease, Oliver cannot escape the conclusion that there must have occurred a shift in the normally predominating glomerular functional balance towards a condition of increased tubular elimination. The structural evidence which compels this conclusion is dependent on the demonstration of: 1, aglomerular tubules; 2, marked hypertrophy and hyperplasia of proximal convolutions; and 3, a shift in the circulation of the blood from a primarily glomerular distribution to a direct tubular supply.

Bell has recorded his findings in 110 cases of acute nephritis[13a] and in 181 cases of subacute and chronic glomerulonephritis, including lipoid nephrosis.[13b] He objects to the usual tendency of writers to discuss acute nephritis as a clinical entity assuming the underlying pathologic process in the entire group to vary only in intensity and not in character. He divides acute glomerulonephritis into 7 types and 2 of these into additional subtypes. The initial glomerular lesion in the most common type, which he calls acute proliferative glomerulonephritis, is described as consisting of an increase of endothelial cells and a splitting and fragmentation of the central capillary basement membranes in the interior of the lobules, the latter being demonstrated by means of special stains. Azotemic glomerulonephritis is characterized by obstruction of the glomerular capillaries whereas in hydropic glomerulonephritis (lipoid nephrosis) the capillary walls are injured but the lumens remain open. This last type of lesion is considered characteristic of membranous glomerulitis.

Physiology of the Kidney. A somewhat abbreviated summary of the current concept of the physiology of the kidney as contained in the writings of Smith,[74] Richards[61] and Hayman[37] seems in order at this point. The beginning of urine formation in man "consists in the separation of the protein-free filtrate of plasma by a purely physical process of filtration, the energy being derived from the heart. As this filtrate flows down the tubule, it is elaborated by the active reabsorption of water, glucose, chloride, sodium and other substances, by the diffusion of a fraction of such waste products as urea and uric acid back from lumen to blood as a result of the concentration gradient established by the reabsorption of water."[37] In addition, such foreign substances as phenol red (phenolsulphonephthalein), Hippuran and Diodrast are secreted by the tubule cells, as is creatinine under certain circumstances, and presumably ammonia and hippuric acid. In amphibia, the reabsorption of sodium chloride appears to be a definite function of the distal convoluted tubule, whereas glucose is reabsorbed almost entirely by the proximal tubule. Although some reabsorption of water occurs throughout the tubule, evidence indicates that it is maximal in the thin segment.[74]

Inulin, a polysaccharide of high molecular weight, is eliminated entirely by glomerular filtration and is neither excreted nor reabsorbed by the tubules.[74] Consequently, its rate of excretion divided by the plasma concentration will be equal to the volume of the glomerular filtrate. Measured in this way, the average rate of glomerular filtration in the ideal man (1.73 sq. meters) is about 120 cc. per minute.[74] The filtration rate in normal man is essentially constant, and regulation of water excretion is effected primarily by regulation of the fraction of water reabsorbed by the tubules.[74] When creatinine is determined by newer analytic methods, the endogenous creatinine clearance is found to be equal to the inulin clearance and its use as a measure of glomerular filtration is advocated.[77] Simultaneous determination of the clearance of inulin and some test substance will enable one to calculate the degree of reabsorption or excretion of the test substance by the tubules. Thus the urea clearance is less than the creatinine clearance, indicating that urea reënters the blood from the tubule; on the other hand, the clearances of exogenous creatinine, phenol red, Hippuran and Diodrast are

greater, indicating that these substances must in part at least be excreted by the tubules.[74] Extensive studies based on this principle have been made in humans by Smith.[74] Other investigations have shown that the process of tubular excretion of certain substances is limited by the circumstance that a given mass of renal tissue can transport from blood to urine only a fixed, maximal quantity of a particular solute per unit time. The measurement of excretion for any one substance constitutes therefore a measurement of what may be called the "tubular excretory mass" of the kidneys.[75] The maximal rate of excretion is different for each substance. The highest yet obtained is that of Diodrast, and consequently, the Diodrast clearance may be used to express the minimal renal plasma flow, or by calculation the minimal renal whole bloodflow, which has been found in man to average 1300 cc. per minute.[75] By the use of these methods, it has been determined that the renal bloodflow is controlled predominantly by the efferent glomerular arterioles, these arterioles being normally partially constricted. Since, with efferent control, an increase or decrease in renal bloodflow is accompanied by an inverse change in filtration pressure, the filtration rate tends to be independent of the renal bloodflow.[23]

Information obtained by the above methods in the study of the diseased kidney will prove valid only if the difference in function between the normal and the diseased organ is quantitative and not qualitative. That this cannot be tacitly assumed is implied by the anatomic studies of Oliver already described,[57] and by his demonstration of the altered handling of the dye trypan blue by the tubular cells of the kidney in naturally occurring canine nephritis.[58]

Kidney Function Tests. The tests of renal function that continue to prove of practical usefulness are the tests of urinary concentration, phenolsulphonephthalein excretion and urea clearance;[11,79] less widely used is the quantitative study of the urinary sediment by the method of Addis.[10] The techniques of these procedures can be found in standard texts and need not be detailed here.

Other tests have been recently recommended, such as the orthotolidine test for hematuria[10,29] and a test of the concentrating power of the kidney which obviates the necessity of a period of water deprivation by the use of pituitrin.[76] For determination of the rate of glomerular filtration an adaptation of the inulin clearance suitable for clinical use has been advanced[4,52] as has also the endogenous creatinine clearance test, using improved methods for the analysis of creatinine.[77] Since the product of the plasma creatinine times the glomerular filtration rate is found to be relatively constant, a simple method for estimation of the glomerular filtration rate is suggested, that is, by dividing 86 by the plasma creatinine concentration.[77] Others consider the level of the plasma creatinine alone to be a sensitive index of kidney function.[6]

Pathologic Physiology of Glomerulonephritis. Recent additions to our knowledge of the pathologic physiology of glomerulonephritis have been obtained chiefly as a result of the application of new methods to the study of old problems, although, as might be expected, new problems have been unearthed in so doing.

The investigations of Burch[18] explain why edema may appear first in the eyelids when there is a cause for generalized edema such as glomerulonephritis, and why it should accumulate during sleep. Whereas the

subcutaneous tissue pressure in the lower eyelid is approximately the same as that of the volar surface of the forearm the skin distensibility of the eyelid is much greater, and the subcutaneous tissues can accommodate a much greater volume of injected fluid for the same rise in tissue pressure. Direct studies indicate that linear rate of lymph flow in the eyelid is decreased by assuming the recumbent position and by lack of blinking, thus explaining the appearance during sleep and the disappearance on waking and rising. Also, the venous pressure in the eyelid is greater in the recumbent position than in the erect. Experiments in dogs suggest that the lower lid serves as a reservoir to take care of any increase in volume of interstitial fluid within the entire orbit.

The presence of an antidiuretic factor detectable by rat bio-assays in the urine of patients with acute nephritis, the nephritic syndrome, and other types of edema has been reported.[63] In some cases this factor was found to be absent after recovery from edema.

Hypertension in acute glomerulonephritis has been attributed chiefly to vasospasm following calorimetric studies of bloodflow during and after the hypertensive phase.[7] The relation of the hypertension of glomerulonephritis to the number of patent glomeruli has been investigated.[39] When less than 700,000 glomeruli per kidney are patent (normal 1,250,000), the systolic blood pressure is invariably above 150 mm. Hg. Below this critical level, no correlation is evident.

Although it is often stated that the specific gravity of the urine tends to be high in acute glomerulonephritis, a special study of this point indicates that the capacity of the kidney to concentrate urine may be definitely impaired.[34]

Determinations of the blood volume by the Gibson-Evans method in Bright's disease[35] reveal that plasma volume tends to vary directly with the serum albumin concentration and blood non-protein nitrogen level, and indirectly with the degree of anemia present. The total blood volume is below normal in all stages of the disease. When congestive heart failure occurs in chronic nephritis the levels of plasma and total blood volume are above average levels for comparable situations without heart failure.

There seems to be convincing evidence that in the nephrotic state protein in the plasma albumin fraction is altered; this has been demonstrated by a quantitative precipitin method[30] and by electrophoretic analysis.[46] Similar alteration in urinary albumin has been observed.[46] The significance of the albumin-globulin ratio of serum in the light of newer knowledge of the serum-protein complex has been considered in a recent report.[51]

Farr has summarized his many contributions to the understanding of protein metabolism in the nephrotic child.[24] The minimum nitrogen requirement necessary to insure positive nitrogen balance has been found to be 2.5 gm. of protein per kilo ideal body weight, nitrogen assimilation reaching a maximum at 3.5 gm. Dietary protein at the level 2.5 to 3.5 gm. per kilo ideal body weight over periods up to 6 years produced no deleterious effects on kidney function. Although feeding an optimal protein diet might be followed by positive nitrogen balance and freedom from edema, rise in plasma-protein concentration was not regularly produced. A period of negative nitrogen balance even on optimal diets was observed to precede acute clinical episodes termed

"nephrotic crises" with or without demonstrable infection such as pneumococci bacteriemia or peritonitis. Since transfusion therapy failed to alter the outcome, study of other factors in nitrogen metabolism was undertaken. For the first time it was demonstrated that the nephrotic patient exhibited a persistent hypo-amino-acidemia, with acute hypo-amino-acidemic crises accompanied by severe clinical manifestations when the level of plasma amino-acid nitrogen fell below the critical level of 2.5 mg. per 100 cc. A sharp rise attended clinical recovery. Amino-acid therapy by means of casein hydrolysate injected intravenously up to 2.25 gm. amino-acids per kilo ideal body weight per day did not influence the chronic hypo-amino-acidemia nor the hypo-proteinemia in spite of the fact that the casein hydrolysate was not excreted in the urine but was retained and utilized and was capable of replacing up to 57% of dietary protein nitrogen. In the crises of acute hypo-amino-acidemia, on the other hand, casein hydrolysate was of great clinical benefit and by this mode of treatment alone, without serotherapy or chemotherapy, mortality was reduced from the previous figure of 66% to zero in 11 cases of pneumococcal bacteriemia.

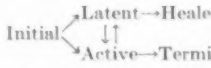
Studies of the mineral metabolism in chronic nephritis[12] have reemphasized the possible harmful effect of diets high in sodium in promoting retention of fluid and elevation of blood pressure. The acid ions, phosphate and sulphate, whereas they promote diuresis and lowering of blood pressure, may lead to acidosis and an aggravation of the renal state, and are to be avoided in the terminal stages of nephritis.

The possibility that the azotemia of renal insufficiency might be due to normal or increased reabsorption by the tubules in the presence of decreased glomerular filtration has been denied as a result of experiments in which the urea clearance was studied simultaneously with the inulin or endogenous creatinine clearance.[5,22,77]

Harrison and Mason[36] have reviewed the pathogenesis of the uremic syndrome. The various theories which have attempted to explain the manifold symptoms of uremia on the basis of some single toxic compound are not supported by adequate proof. The etiology is undoubtedly multiple. A known and definite rôle in the pathogenesis of uremia can be ascribed to a few substances. Calcium ion deficiency as a result of the retention of products forming un-ionized calcium salts is concerned in the initiation of motor irritative phenomena; phenol derivatives are related to the stuporous state; accumulations of organic and inorganic acids, as well as loss of base, play a rôle in the production of respiratory disturbance; depletion of chloride and of water increases the catabolism of protein and at the same time impairs further the ability of the body to excrete the resulting metabolites. There is strong evidence that other substances are also of pathogenetic significance. Guanidine-like compounds occur in excess in the blood and seem to play a rôle in the production both of motor irritative phenomena and of gastro-intestinal disturbances. Urea accumulation may be harmful either by initiating excessive fermentation in the alimentary tract, or by interfering with the processes of detoxification. As an index of uremia, a high xanthoproteic reaction of the blood and a high indican content are considered more valuable than the level of the blood-urea nitrogen.[42]

Clinical Aspects. As stated by Longcope[45b], "a knowledge of the natural history of any disease is best obtained by observing the process from its

onset through the subsequent phases of its activity to its termination in recovery or in death. This method is a difficult one to pursue in a condition such as nephritis . . . . which may last for many years." Certainly in no other disease is an understanding of the natural history of greater importance than in glomerulonephritis, with its tendency towards explosive or insidious onset, prolonged latency or chronic activity, and eventual healing or fatal termination. Of great aid in portraying this picture is the familiar diagram of Addis[15] or its modifications:



Acute glomerulonephritis may occur at any age but is more common in childhood than in adult life. The ratio of males to females is 2 to 1.[68] Rarely glomerulonephritis may appear in several members of one family.[62] In Longcope's series[45b] of 141 patients, chiefly adult, the disease commenced with the typical acute onset in 87.5% and insidiously in 12.5%.

In nephritis of acute onset, the predominance of one or another finding justifies the division into syndromes[54] as follows: *a*, urinary syndrome; *b*, hypertension; *c*, edema; *d*, nitrogen retention; and *e*, true uremia. The incidence of certain manifestations in two series[38,54] respectively is: gross hematuria, 40%, 32%; edema, 58%, 57%; nitrogen retention, 43%, 44%; and uremia, 7%, 7%.

The hypertensive syndrome might well be called the cardiovascular syndrome, for many recent studies[38,50,54,80] have emphasized the importance of cardiac insufficiency in acute nephritis. It is not necessarily related to arterial hypertension and may be recognized by dyspnea, pulmonary congestion, cardiac enlargement, gallop rhythm, elevation of venous pressure, slowing of the rate of circulation, enlargement of the Roentgen shadow of the heart and changes in the electrocardiogram. Circulatory insufficiency has been noted in 53 of 59 severe and in 12 of 35 mild cases of acute glomerulonephritis.[80] The electrocardiographic findings, summarized by Williams[81] from 15 personal cases and 70 cases from the literature, consist chiefly in lowering or inversion of *T* waves, prolongation of the *P–R* interval and slurring of *QRS*. No correlation could be established between the occurrence of these changes and the signs of cardiac or renal insufficiency.[81] The myocardial involvement in acute nephritis is considered by some[80] to be an expression of the widespread capillary damage occurring in this disease.

The characteristics of glomerulonephritis of insidious onset, without known antecedent infection, have been presented by Longcope.[45b] Admitting that this type might quite possibly represent simply the active stage in the progress of glomerulonephritis of unrecognized onset, on the other hand, there would seem to be certain differences which distinguish this from the ordinary type, namely, a higher rate of unfortunate outcome, a lower incidence of skin reactions to streptococcal filtrates, and a lower incidence of elevated antistreptolysin titers.[45b]

An important feature of glomerulonephritis is the tendency towards exacerbations of the disease, usually marked by an abrupt increase in hematuria. As emphasized in a recent study[69] such exacerbations are almost invariably preceded by some infection, usually with Group A streptococci. Curiously, in this study, reduction of renal function in such flare-ups was not invariable and seldom permanent.

Following the acute phase of glomerulonephritis latency or chronic activity may persist for years and careful study of the urine, blood pressure and kidney function at frequent intervals over long periods of time may be necessary to determine whether healing or activity is occurring, especially in those cases where such decision is not made obvious by progression into the terminal stage.

Prognosis. Collected statistics[38,47b] indicate that the mortality rate of acute glomerulonephritis is fairly uniform in all series and averages 5% to 9%. There is no such uniformity of statistics as regards the eventual outcome beyond this stage, except for general accord in the better prognosis in childhood. Longcope[45b] estimates the recovery rate for children to be 60% to 75%, and for adults 40% to 60%. The final classification as to outcome in any series depends greatly on the length of time followed and the completeness of the examination. In 495 cases collected from 7 reports[38] (followed 6 months to 14 years) the percentage of those said to be cured was 43% to 85%, latent 17% to 32%, and chronic 4% to 42%.

What are the factors that determine the prognosis in an individual case? Addis has stated that in this disease the end is determined by the beginning.[1c] Yet the severity of the acute phase is apparently not of importance, except that where a definite infection is known to precede the onset of nephritis the prognosis is better.[45b] The type of infection may have some bearing since it has been shown that healing of the renal lesion occurs in 90% of cases in which the preceding infection has involved the skin.[27] As stressed by Addis[1b] and others[38,60] of great importance in forecasting an unfavorable termination is the failure of healing to become apparent within 1 year. The persistence of foci of infection is considered by some[45b,47b] to play a rôle in the progression of the renal lesion, and in support of this contention might be brought forward the relatively better prognosis where nephritis has followed infections of the skin, since the latter can nearly always be eradicated. In refutation of those who would remove all infected foci is the study of Illingworth[40] who failed to find early or late beneficial effects of tonsillectomy in 119 children subjected to this procedure during the acute phase of the disease. As has already been mentioned, exacerbations of glomerulonephritis are reported to produce only transient decrease in renal function in most cases. Thus, there is at present no final answer to this most important question of the factors concerned in the ultimate prognosis of glomerulonephritis.

Once complete healing of the renal lesion has been accomplished, it is most unusual for acute nephritis to recur, even following streptococcal infections.[44]

Treatment. As regards prophylaxis, although the most frequent illness antecedent to nephritis is infection of the upper respiratory tract, and especially tonsillitis, it has been shown statistically, that tonsillectomy cannot be relied upon to prevent glomerulonephritis, and indeed it may even precipitate the development of this lesion.[40] It is possible that the widespread use of the sulfonamide drugs will reduce the duration, the severity, the number of complications and perhaps the incidence of hemolytic streptococcal infections, and in so doing reduce the incidence of acute glomerulonephritis.

A discussion of the treatment of the disease itself should properly

begin with a consideration of the question as to whether or not anything can be done to alter the course of the renal lesion once it has become established. Some of the factors concerned in this problem have already been discussed under the heading of "Prognosis." Regarding removal of foci of infection, little is to be gained by adopting the hopeless attitude, and it would seem wise to follow the recommendations of those who believe that persistence of infection spells progression of nephritis. Investigation of the value of the sulfonamide drugs is in progress.[45b,47b] If there exists an active hemolytic streptococcal infection, their use would seem indicated, and sulfanilamide has been given in reduced dosage without ill-effect where the blood level of the drug has been carefully watched.[45b] Surgical measures such as mastoidectomy may become necessary for intrinsic reasons during the acute stage, but it is generally considered advisable to defer tonsillectomy or drainage of sinuses until the acute manifestations have subsided, since an exacerbation at least in the urinary findings, may follow these procedures.

The possibility exists that dietary factors may play a rôle in determining the course of the renal injury. Although clinical studies[20,49,56] have failed to reveal any deleterious effects of proteins, in experimental acute renal insufficiency (produced by nephrotoxic serum,[72] vena caval obstruction,[2] partial,[21] and complete[14] nephrectomy) it has been demonstrated that diets high in protein are harmful, and may, in certain, but not in all, species of rats[73] be responsible for progression in nephrotoxic nephritis. On the other hand, diets high in carbohydrate have been found to be beneficial.[14,21] The value of the alkaline-ash diet, long recommended, has been questioned.[53] Alcohol apparently does not aggravate the renal lesion in glomerulonephritis.[16]

Except for the enforcement of rest and quiet in all instances, treatment of the acute attack cannot be standardized. Individual items of therapy must be employed with a clear knowledge of the pathologic physiology in the particular case at hand. Protein should be limited especially when azotemia is of significance. The intake of fluid and salt should be restricted when hypertension and cardiac failure are prominent, but increased when azotemia is severe. Digitalis may prove useful in myocardial insufficiency.[80] Magnesium sulphate intravenously or intramuscularly (0.2 cc. of a 25% solution per kilo) and by mouth has proven effective in reducing the blood pressure, apparently by combating vasospasm.[64] Cerebral edema and convulsions may be relieved by sedation, spinal drainage, or the administration of 50% sucrose intravenously. Severe oliguria and anuria may be serious problems and an evaluation of the effectiveness of such measures as diathermy and the intravenous use of hypertonic sugars is difficult. The length of time that bed rest should be enforced following an attack of acute glomerulonephritis is a matter of judicial individualization. It would seem wise to advise bed rest as long as steady improvement progresses and to discontinue it only when no further improvement is apparent.

In the chronic active stage of glomerulonephritis including the nephrotic syndrome, edema is usually the most troublesome manifestation. Diets high in protein (100 to 120 gm. for adults, 3 gm. per kilo for children) are necessary in order that protein lost in the urine may

be replaced. The intake of fluid should be restricted and diuretic salts, such as ammonium or potassium chloride or nitrate, or ammonium sulphate[2] should be substituted for sodium chloride. The use of acacia to promote diuresis has been studied extensively,[31–33,43,70] and found to be effective and safe if properly employed. Its diuretic effect is attributed to the increased excretion of water and chloride that follows its injection.[32] It may be administered as a 6% solution of acacia in 0.9% sodium chloride,[43] 500 cc. or 30 gm. being given daily until a total of 120[31] to 180 gm.[43] has been given. Before acacia is used, patients should be tested carefully for sensitivity.[42] Urticarial reactions occur in 10% of cases, are usually relieved by epinephrine and are not considered a contraindication to further therapy.[31] More serious reactions accompanied by dyspnea and chest pain occasionally occur and are indications for discontinuance of the injection. Alarming increase in blood volume has been observed,[43] and fatalities following the use of acacia have been reported and attributed to liver damage and the blockage of capillaries by conglutination of red blood cells.[78] Concentrated human blood serum has been found to be an effective diuretic in nephrosis but not in other types of renal edema.[3] As previously mentioned, intravenous amino-acid therapy by means of casein hydrolysate is reported to be of great value in lowering the mortality of the "nephrotic crisis."[24]

In the terminal stage of glomerulonephritis with increasing azotemia, dietary protein should be limited and fluid intake increased, unless congestive heart failure is present. Acidosis may be relieved by the use of sodium bicarbonate and twitchings may be abolished by the injection of calcium salts.[36] Hyperphosphatemia with its attendant hypocalcemia may respond to diets low in phosphorus or to the oral administration of aluminum hydroxide which decreases the absorption of phosphorus from the bowel.[26] Therapy thus is aimed at the relief of disturbing symptoms, or, as Page has expressed it in an excellent review of the therapy of Bright's disease,[59] "treatment in the terminal stage consists first and foremost in making the patient happy."

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NEUROLOGY AND PSYCHIATRY.

UNDER THE CHARGE OF

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ELECTRICALLY INDUCED CONVULSIONS IN THE TREATMENT OF MENTAL DISORDERS.

In recent years "shock" treatment of mental disorders has been both enthusiastically promoted with optimistic claims and harshly condemned as unscientific and barbaric. Careful clinical studies have somewhat deflated some of the earlier claims,[22] but have at the same time indicated that shock treatment is a valuable method in a more limited sphere. It has been emphasized repeatedly that shock treatment of any sort should be only a small part of the total therapy in any case of personality dysfunction.[9,21a,28,35]

While the perfection of certain details in procedure has decreased the immediate dangers connected with insulin[16,32] and metrazol[3,8,9] therapy, the serious question of the possibility of later organic brain damage is still unanswered. However, despite a lack of carefully controlled and independently verified investigations of these therapeutic instruments in experimental laboratories, widespread clinical application of shock treatment has been made and will no doubt continue for some time. The rapid development of shock therapy reflects the increased concern over the enormous personal, social, and economic importance of mental disease in general, a problem of the first magnitude.

Even with many basic problems of insulin and metrazol therapy still undecided,[22] various other agents of similar nature have been given clinical trials. Among these are other convulsant drugs,[9] inhalation of nitrous oxide[14] and nitrogen,[38,39] and the production of convulsions by the application of the electric current.

Of these, electric shock therapy is the most important and has already been given extensive clinical use in mental disorders.[30] Although it has been reported to present a number of advantages over other types of shock therapy, it is noteworthy that reports of therapeutic results with electric shock have tended to be more conservative than the earlier reports about insulin and metrazol. It should be understood that electric shock therapy is a form of convulsion treatment with general effects similar to those of metrazol, and that insulin treatment is a less acute, more prolonged method in which the production of convulsions is not necessarily desirable.[16] Chemotherapeutic methods of shock therapy were reviewed in these columns in December, 1937,[28] and in December, 1939.[9] Other excellent reviews have been published recently by Katzenelbogen[22] and by Jessner and Ryan.[27] This paper deals primarily with electric shock therapy.

For nearly 40 years it has been known that convulsions and unconsciousness can be produced in animals by the application of electric current by various methods,[4] and the dramatic accidents with electricity in humans are an everyday commonplace. Convulsive seizures of a restricted nature have been produced frequently in humans by direct electrical stimulation of the brain at operation. Experimentally, the use of electrically induced convulsions led to the discovery of the anticonvulsant effect of diphenylhydantoin by Putnam and Merritt in 1938.[46]

The first therapeutic use of convulsions induced by electric current was reported in 1938 at the Medical Academy in Rome by Cerletti and Bini, following animal experiments to determine a safe method.[6a] Since introduction of the treatment into England in the following year and more recently into this country, several different types of apparatus have been devised, but all are essentially the same in principle.[11,13,45,50,51]

Current is passed through the fronto-temporal regions by way of large metal electrodes held firmly in place on each side of the head by means of either a tight rubber band or large forceps resembling ice tongs. Ordinary 110 volt alternating house current may be used as the source; the voltage is regulated by transformers, and the duration is regulated by an automatic timer.

For optimal conduction electrode jelly is vigorously applied to the scalp, and the electrodes are covered with cloth jackets soaked in strong (20%) salt solution. The centers of the electrodes should be placed not further back than the coronal suture and the edges should not extend below the orbito-meatal line. The electrodes should be as far apart as possible within these limits. This site of application has been found to be the most satisfactory;[24b] it is believed that the frontal adversive field (area 6aB of Vogt and Brodmann) is the area with the lowest convulsive threshold.[13,29] Application further back might lead to undesirable medullary stimulation, and application further forward has been found to be less efficient.[24b] Large electrodes with an area of 30 to 100 sq. cm. are used to prevent burning of the scalp and are also thought to be more efficient than smaller electrodes.[24b,30]

Before application of the shocking current the intactness of the apparatus is tested by the passage of current through an "artificial head," a conductor of known resistance. Then a trial current of very low voltage (0.5 to 1 volt), imperceptible to the patient, is passed through the patient's head to determine the relative resistance of the head. The apparent resistance as measured in this manner ranges from 400 to 2000 ohms; a resistance of more than 2000 ohms usually indicates inadequate contact between the electrodes and the scalp.[51] The actual resistance of the head during the passage of the higher voltage shocking current is known to be considerably lower than the resistance determined beforehand with the low voltage testing current.[20,24b,30,51]

This alteration of the resistance is believed to be due to changes in the superficial tissues of the head brought about by the higher tension current.[24b] It has been shown that patients with initially high resistance have a proportionately greater fall in resistance than patients whose resistance is initially rather low.[24b]

No true correlation exists between the initial resistance readings and the convulsion threshold of the patient. Most patients show a slight

day-to-day variation in threshold, and it is usually necessary to increase the dosage of current slightly during successive treatments.[26] The amount of electricity may be regulated by changing either the voltage or the duration of the shock.

The usual voltage range varies from 70 to 150 volts, and the duration of exposure varies from 0.05 to 2 seconds. The amount of current passed through the head varies from 300 to 1000 milliamperes, but it is said that only about one-hundredth of this amount actually reaches the brain.[24b] A voltage of less than 60 produces a stimulus so small that the patient does not lose consciousness and may feel the shock. Although shocks of much higher voltage and longer duration than any obtainable with the usual apparatus may result in serious damage of the brain,[6a,b] it is believed that no harm results from using an overstrength stimulus within the above maximal voltage and duration.[24b]

The course of treatment is usually started with a setting of 80 to 130 volts at 0.1 to 0.2 second. If a satisfactory seizure occurs, the same setting may be used the next time. If no convulsion at all occurs, another stimulus may be given immediately with increased voltage or duration, successively stronger shocks being given until a convulsion is induced. Hemphill and Walter[24b] have given as many as six shocks in succession without mishap. Rare patients have a very high convulsion threshold (up to 150 volts at 0.6 second), but it is practically always possible to secure a convulsion. It is never necessary to use a setting of greater than 150 volts.

With proper procedure there is always instantaneous and absolute loss of consciousness following the application of the stimulus.[26,48a] An inadequate stimulus produces an "absence" or stunning reaction. This may consist merely of momentary unconsciousness with a sudden start but no muscular contractions; the patient may experience some peculiar sensation such as "flashes of light" but feels no pain.[2] A larger but still subconvulsant stimulus produces a "petit mal" reaction, characterized by a sudden start and immediate unconsciousness for 5 to 40 seconds, with occasionally facial twitchings, coarse arm and leg tremors, apnea, cyanosis, and confusion of brief duration.

The "grand mal" convulsion type of reaction closely resembles a true epileptic seizure and is similar to a convulsion produced by metrazol but is of shorter duration and lesser severity. There is an immediate loss of consciousness and a start, a sudden marked generalized flexion movement, thought to be due to direct stimulation of the motor cortex. A cry occurs frequently but not always. The generalized tonic spasm, which lasts from 10 to 25 seconds, may occur immediately or, less commonly, following a latent period up to 30 seconds.

The clonic phase, lasting from 10 to 30 seconds, then ensues. The pupils become widely dilated, and there is conjugate deviation of the eyes. During the convulsion the patient does not breathe and usually becomes very cyanotic. The total apneic period is usually less than a minute, and delayed resumption of respiration is quite rare.[49] Incontinence is rare; ejaculation has also been reported. After the convulsion there is a short period of deep stupor, often with sucking or biting movements, and then a period of confusion, seldom lasting longer than 10 minutes.

For a short period following the convulsion there is usually a moderate

rise in the systolic blood pressure and a tachycardia which is occasionally followed by a bradycardia. Ankle clonus is almost always present, and Hoffmann's and Babinski's signs frequently appear for a few minutes. The blood sugar usually rises about 50%, the red cell count and hemoglobin are slightly elevated, and the white cell count may be doubled soon after the convulsion; these changes usually return to the previous level within ½ hour. There is always a marked increase in the lactic acid content of the blood after a convulsion,[21a,27] undoubtedly due to the muscular activity.

There is always a complete amnesia for the period of treatment.[53] Some patients have a complete retrograde amnesia during which they are unable to recall any event which transpired during a period of 2 or 3 hours preceding the shock. In others, this amnesia is partial or insular in type, while some patients have only a mild and transitory amnesia of events immediately preceding the shock.[33] Some patients also show a patchy impairment of memory separate from the amnesia associated with the treatments. This memory loss is usually transient and does not disturb the patient, although occasionally it may last as long as 2 months after the last treatment.[19]

Preparation of the patient for the treatment is relatively simple.[30] The treatment is usually given in the morning, and breakfast should be withheld, although nausea and vomiting following electric shock treatment are much rarer than following metrazol. The bladder and bowels should be evacuated before the treatment. If a sedative drug is administered during the night preceding a treatment, the convulsion threshold may be raised.[24a,48b] It is not necessary to shave the patient's head, but all hairpins and other metal objects should be removed. A mouth gag should be inserted initially to prevent biting of the tongue, and artificial dentures should be removed. The assistants who hold the patient are in no danger of receiving a shock, providing the patient's head is not touched during the passage of current, and that they are standing on a dry floor.

To prevent fractures and dislocations the treatment is given with the patient reclining on a hard, flat non-metal table or couch, free of moisture. A small hard pillow or sandbag is placed under the midthoracic region of the spine, while the patient's shoulders, hips, and knees are fixed to the table by firm pressure.

This method of spinal hyperextension has been found to reduce considerably the incidence of vertebral fractures in patients treated with metrazol.[8,18,22] Curare has been employed most successfully for the prevention of fractures in metrazol therapy, but Kalinowsky and his coworkers[31] advise against the use of curare for this purpose because electric shock treatment has—contrary to metrazol—a depressant effect on the respiratory center. Furst and Stouffer,[19] however, report the use of curare without mishap in 5 electrically treated cases.

The optimal frequency and total number of treatments in a course are as yet undecided. Most workers recommend that the treatment be given 2 or 3 times a week up to a total of 10 or 15 treatments. Furst and Stouffer[19] state that despite improvement after 3 or 4 treatments, the course should be continued to 10 in order to "fix" the result. Gonda[21a] believes that more treatments may be necessary to schizophrenics than in depressed patients, and advises 20 or more shocks in

schizophrenics, even though improvement has appeared after a few treatments.

Sogliani[49] describes cases in which the improvement started only after the 30th convulsion and some even later. Both Sogliani and Fumarola[17] have given some patients repeated convulsions in a single day in an effort to reduce the duration of the course of treatment. Hemphill and Walter[24b] see no harm in giving the treatments daily for 60 or more days in some cases while there is any hope for more improvement.

On the other hand, Myerson[44] believes that as few shocks as possible should be given, that only 3 or 4 treatments may be required for a complete remission in some patients with depression. Ziskind's work with metrazol indicates that a course of 2 treatments a week for 6 to 8 weeks carries little danger of memory impairment, and 3 treatments a week should not be given for longer than the first 2 weeks.[54]

So far, reports on the results of electric shock therapy show no essential differences from the recent results with metrazol.[36,44,47,49] The best results have been obtained in depressions, with only fair results in acute schizophrenia. Most observers have reported more than 70% or 80% remissions or marked improvement from depressions.[7,19,21a,42,44,53] Good results have also been obtained in the small number of manic patients treated by different workers.[24b]

Sogliani[49] reported "recovery" in 12 out of 15 schizophrenics with illness of less than 1 year's duration, but in only 3 out of 55 cases of more than 1 year's duration. As with metrazol, the best results have been reported in the catatonic group, but in all types of schizophrenia early relapses have occurred in a large percentage of cases.[47] Wyllie[53] obtained "immediate improvement" following electrically induced convulsions in 14 out of 18 schizophrenics, but in only 2 cases was the improvement maintained for as long as 2 months.

Others have reported remissions varying from 21% to 80% in cases of schizophrenia of recent onset.[19,21a,31,42] It is generally agreed that results with chronic cases are much more unfavorable, but some advise the use of electric shock therapy in chronic institutional cases of schizophrenia to facilitate their general management.[24b,31] Such reports indicate that electric shock, as well as metrazol, is probably not a very useful type of treatment for schizophrenia, except that in some cases it may bring about a change which facilitates other forms of therapy and accelerates recovery.

No deaths have been reported yet from more than 10,000 electric shock treatments.[30] The complications and contraindications are apparently similar to those for metrazol. Exacerbation of chronic pulmonary tuberculosis has been the chief cause of death following metrazol therapy.[5,34] Although this is unexplained, there is no reason to believe that electric shock therapy will be less dangerous in this respect. Fractures and dislocations have been reported following electric shock therapy,[7,20,21a,b,53] but less frequently than after metrazol, probably because of the somewhat milder character of the convulsions.

The treatment is contraindicated in the presence of active or recently healed pulmonary tuberculosis or other disease of the lungs, any febrile illness or acute infection, arthritis of the spine, marked hypertension

or arteriosclerosis, serious cardiac disease, nephritis, or organic disease of the central nervous system.[7,24b] These contraindications may have to be modified in individual cases with mental conditions so desperate as to threaten life.

Aside from the lessened danger of fractures, dislocations, and muscle injuries, electric shock therapy has a number of other advantages over metrazol.[1,6a,b,11,15,21a,26,48b,49] Other complications are also less frequent: headache, nausea and vomiting, and severe psychomotor excitement are quite uncommon after electric shock.

The milder nature of the convulsions with electric shock produces less strain on the cardiovascular system than either insulin or metrazol. Bellet, Kershbaum, and Furst[2] studied the electrocardiograms of 50 patients with 100 electric shock treatments and found only minor changes, except 2 records of older patients in whom more serious signs were encountered.

Another marked advantage is the absence of the "fear" reaction or aura which invariably occurs with metrazol during the latent period between the injection and the loss of consciousness and also prominently with subconvulsant doses.[21a] However, despite the complete amnesia for the electric shock and absence of a fearful aura, some patients dislike the treatment because of their ignorance about what has happened to them, but seldom object greatly to subsequent treatments.[44,53]

Most patients are more coöperative in electric shock therapy than with metrazol. An uncoöperative patient can be "stunned" by a preliminary subconvulsant shock in order to facilitate proper holding for the treatment itself.

The difficulty in making an intravenous injection in an uncoöperative patient or in one with inaccessible or thrombosed veins, so common in metrazol therapy, is entirely escaped by electric shock. The effects of a blood-borne drug are avoided, and delayed reactions, not uncommon following metrazol, are very rare after electric shock, although a few serious delayed reactions have been reported.[2,41] After the instrument is purchased initially the cost of the treatment is negligible, and as many as 15 or 20 patients can be treated in 1 hour.[24b]

These advantages of electric shock therapy constitute in themselves a serious but indirect danger, if the method is to be put into indiscriminate and promiscuous use by unqualified and misguided therapists. Shock treatment in general is still in an experimental stage with an uncertain future.[10,37] All forms of shock treatment are believed to produce qualitatively similar types of organic brain damage in animals.[23,52a]

Weil and Liebert[52a,b] reported marked glial changes and mild neuronal lesions in the brains of 6 patients who had received metrazol treatments several months previously, and also found similar disturbances in the brains of rabbits subjected to either metrazol or insulin treatments. Finley and Brenner[12] observed similar lesions in the brains of monkeys treated with insulin or metrazol.

Bini[4] found widespread and severe but mainly reversible changes of the cortical nerve cells of animals subjected to electric shock similar to that used in treating humans. Heilbrunn and Liebert[23] made biopsies of brains of rabbits at intervals following convulsions produced by various agents. They found that the changes in the ganglion cells

were more severe following electric shock than after metrazol, insulin, camphor, or nitrogen gas. They also noted that reversal of the morphologic alterations occurred more slowly after a second or third convulsion than after the first.

Studies of electroencephalograms of humans and animals indicate that changes in cortical activity are usually of shorter duration and milder following electrically induced convulsions than after metrazol convulsions.[1,13,25,40] However, it was noted by Hughes, Wigton, and Jardon[25] that after successive convulsions during a series of treatments, abnormal electroencephalographic waves persist for longer periods, so that after 6 or 7 treatments they may be observed for several days and occasionally may not entirely disappear for 2 or 3 weeks after the last treatment. Such observations show the need for much more clinical and experimental studies of similar nature.

The possible efficacy of subconvulsant or petit mal shocks should also be considered.[19,43] A few observers believe that some patients may be made worse instead of being helped by subconvulsant shocks.[50] Electric shock has also been used as an outpatient procedure with apparent safety.[24,5,44,50] This practice should not be adopted generally until the effects of the treatment are better known. Patients whose conditions justify such a form of treatment ordinarily should require hospital care.

Electric shock will probably largely replace metrazol as a form of convulsion therapy.[19,43] This type of treatment is chiefly indicated in depressed states; its value in manic reactions is less certain. In schizophrenia its usefulness is quite limited. The use of such a drastic method in the treatment of the ordinary types of psychoneurosis is not justified in the present state of our knowledge of remote effects.

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PHYSIOLOGY.

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF NOVEMBER 18, 1941.

Labyrinth and Cerebellum. E. Spiegel and N. Scala (Department of Experimental Neurology, Temple University School of Medicine). The following observation may shed some light upon cerebello-labyrinthine relationships.

After inducing a lesion in parts of the cerebellum of cats, particularly in the lobus posterior medianus, with the vestibular nuclei and their fiber systems histologically intact, nystagmus was observed in abnormal positions of the head, particularly in supine position with the vertex downward. When nystagmus in normal position of the head was weak, it was increased, sometimes also its direction was changed, in abnormal positions. In some cases nystagmus appeared in abnormal positions only. This phenomenon is transient. Electrolytic lesions of the nuclei

tecti had a similar effect. In analyzing the receptor mechanism, neck reflexes and retinal reflexes could be excluded. Bilateral labyrinthectomy abolished this effect of position, while a weak spontaneous nystagmus could persist. It is assumed that the appearance of positional nystagmus following cerebellar lesions is a phenomenon of release of parts of the vestibulo-ocular reflex arcs, since it is associated with increase of the experimental postrotatory nystagmus.

Periodicity of the Excitatory Process in Nerve. FRANK BRINK and D. W. BRONK (Johnson Research Foundation, University of Pennsylvania). The cellular mechanism which determines the time interval between propagated impulses in chemically excited nerve cells was studied. Arvanitaki has reported (*Arch. internat. de physiol.*, **49**, 209, 1939) the existence of localized periodic changes in electrical potential at the site of initiation of propagated impulses. In the present experiments, it has been shown that when the calcium and magnesium are removed from the fluid bathing a restricted length of the giant axon of a squid, such periodic electrical discharges occur as the first evidence of excitation at a time when there are no conducted impulses. These local periodic potentials increase in amplitude until, finally, conducted impulses are initiated at the same frequency as the previously initiated local response. Thus the intervals between impulses in a train are determined by a periodic excitatory process that exists independently of the conducted impulses. Adrian's hypothesis that such intervals are determined by a process of recovery from a previous impulse must therefore be reconsidered.

When the calcium was removed from the fluid bathing a limited portion of a myelinated nerve fiber (Type A) a train of propagated impulses was initiated. The time intervals between successive impulses were not always equal. The larger intervals were shown to be approximately integral multiples of the shortest or fundamental period. The departure from the exactness of this rule was related to the random variations in the fundamental period of the excitatory process. It is assumed that this fundamental period of the conducted impulses in these fibers is determined by the periodicity of a local excitatory process similar to that observed directly in giant fibers from squid.

The Effect of Vagotomy on the Secretory Response of the Pancreas to Peptone. J. O. CR'DER and J. E. THOMAS (Laboratory of Physiology, Jefferson Medical College of Philadelphia). The presence in the intestine of products of protein digestion increases the flow of pancreatic juice through a mechanism other than secretin (*Am. J. Physiol.*, **134**, 656, 1941). Presumably a reflex affecting the secretory nerves is involved. In an effort to trace the reflex pathway, dogs were prepared in which either both cervical vagi were chronically exposed or one vagus was cut and the other exposed. In such animals injection of peptone solution into the duodenum had the usual effect of increasing the rate

of secretion of pancreatic juice. After the vagi were blocked by injection of cocaine or procaine into the exposed nerve trunks or by cutting the remaining intact vagus (in 1 animal) peptone, administered as before, failed to increase the flow of pancreatic juice. The conclusion is drawn that peptones stimulate pancreatic secretion through a reflex arc involving the vagus nerves.

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